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MARINE MICROORGANISMS AS A SOURCE OF NOVEL ANTIFUNGALS

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Abstract
Undiscovered natural chemicals having antifungal and antibacterial qualities can be found in understudied environments, such as the world's oceans. The largest ecosystem on Earth is found in the oceans, which are home to a wide variety of life forms. In the past three years, there has been an increased focus on the oceans, and it has been demonstrated that marine species such as bacteria, fungi, algae, sea cucumbers, sea sponges, and others may contain chemicals with antibacterial properties. This review discusses 40 antimicrobial and 56 antifungal compounds found in marine organisms. The chemicals are separated according to their organismal source and chemical structure groupings, such as terpenes, polyketides, alkaloids, and ribosomal peptides. The review lists the bacterial and fungal strains that these chemical compounds are effective against along with their minimum inhibitory concentrations, or MIC values. The study holds great potential for tracking the creation of novel, cutting-edge antimicrobial drugs from these naturally occurring substances that have been isolated and their antibacterial qualities assessed.
Keywords: marine compounds, antibacterial activity, antifungal activity

1. INTRODUCTION

Among the most potent medications used to treat dangerous illnesses are antibiotics. Their presence has greatly improved the health of both people and animals. We are living in a period when incurable illnesses are killing people alive. These conditions are specifically brought on by the development and spread of antibiotic-resistant bacteria [1]. Because they are difficult, if not impossible, to cure, antibiotic-resistant diseases have the potential to be lethal. According to the CDC's 2019 Antibiotic Resistance (AR) Threats Report, disease prevention and control antimicrobial resistance is a significant worldwide public health concern that claims the lives of at least 1.27 million people annually. According to the report, more than 35,000 people die each year in the US from more than 2.8 million antibiotic-resistant diseases. Antibiotic resistance in bacteria is spreading quickly as a result of patients' and healthcare providers' improper and excessive use of antibacterial drugs.

Enhancing the proper use of antibiotics and minimizing their misuse are therefore crucial. The creation of novel antimicrobial products is also crucial for human, animal, and agricultural health. Most newly developed antibacterial drugs in the pharmaceutical sector are semisynthetic derivatives of the original natural material discovered over 50 years ago. Indeed, beta-lactams, macrolides, and quinolones accounted for over 70% of antibacterial drugs granted between 1981 and 2005[4]. Modified natural molecules that are already present have been used to develop compounds that temporarily get around the resistance mechanisms [9]. The development of

completely new natural chemicals is ultimately the only way to overcome bacterial resistance. Most antibiotics discovered in the past half-century have been identified in terrestrial species[2].

Not much focus has been placed on aquatic organisms' ability to create antibacterial chemicals. The largest and most important ecosystem on Earth is the marine environment. It is made up of a vast array of different types of life, from whales to tiny microbes. Therefore, the ocean has the potential to produce novel antibiotics, and studying uncharted marine habitats is crucial to meeting the pressing need for potent new antibiotics. This variety provides a wealth of resources for the particular goal of creating innovative medications that can effectively treat particular illnesses [3]. Finding new antibacterial drug leads is much more likely in the sea than on land.

2. REVIEW OF LITERATURE

Synthetic organic chemistry can offer access to synthetic analogies and large-scale biological screening for the investigation of structure-activity correlations (SAR). Investigating and compiling the antibacterial and antifungal qualities of various chemical compounds that have been identified from marine organisms is the aim of the current project [13]. Known as "chemical gold," marine microorganisms are believed to be an excellent source for new therapeutics. Bacteria are ubiquitous in the maritime environment. They are able to survive in any severe environment by adapting to it. Therefore, in the bioremediation of toxic, heavy metal, hydrocarbon, xenobiotic, and many other resistant substances, marine bacteria frequently outperform terrestrial bacteria[10]. The formation of biofilm and extracellular polymeric substances (EPS) is the cause of this. Large, amphipathic compounds with a tertiary structure (conformation), antimicrobial peptides (AMPs) are produced ribosomally from amino acids. Their broad-spectrum antibacterial effect makes them ideal for attacking the membranes of prokaryotic cells. They differ from the flexible lymphocyte-based immunity found in higher vertebrates due to AMPs.

Bacteriocins are the name given to those AMPs that bacteria release. The AMPs are found inside neutrophils or on the exterior surfaces (skin) of multicellular organisms. Hemocytes, which are cells that resemble neutrophils, contain AMPs in marine invertebrates. Their amphipathic nature may possibly contribute to their antibacterial activity. Some of them avoid various enzymatic and non-enzymatic systems, which contributes to the accumulation of ROS and helps to deactivate free radicals. This has negative consequences that stop the growth of fungal cells [5]. Additionally, there are two ways in which phlorotannins alter the potential of the mitochondrial membrane. Higher amounts of phlorotannin activated the anti-apoptotic defenses of fungal cells. Consequently, the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL increased, reducing oxidative stress and halting cell death. When these anti-apoptotic proteins are produced, the membrane potential stabilizes more quickly.

3. MATERIALS AND METHODS

The search for new physiologically active substances has broadened to include screening species in new environments. In this regard, the seas, which comprise more than 67% of the planet, are fascinating ecosystems that are worth investigating due to their abundance of species. Marine microorganisms are therefore highly intriguing as potential sources of novel bioactive substances that may be advantageous to humans. Complex compounds with intriguing biologically distinct features are created for a variety of commercial and biotechnological purposes since some of them can survive the harsh conditions of the sea. Thus, chemicals with antioxidant, antibacterial, apoptotic, antitumoral, and antiviral properties have been discovered in a variety of marine microorganisms, such as fungus, myxomycetes, bacteria, and microalgae. The separation of bioactive compounds from marine microorganisms that has been documented since 2018 is compiled and discussed in this paper. It also highlights the potential for marine bacteria to produce highly lucrative bioactive compounds. Because oceans offer a wide range of distinct environments with varying salinity levels, hydrostatic pressures, and temperatures, marine bacteria have developed a number of adaptation strategies, including the synthesis of special proteins, to allow them to flourish in these diverse environments. Thus, it appears that marine microorganisms possess a significant capacity to generate beneficial compounds that are absent from terrestrial settings [11].

In particular, extremophilic bacteria evolve distinct metabolic pathways and characteristics in severe marine conditions, which represent novel ecological niches. Invasive fungal infections (IFDs), which are linked to high morbidity and death, have been becoming more common worldwide, particularly among immunocompromised people[6]. The efficacy of existing therapeutic antifungal medications, such as azoles, polyenes, and echinocandins, against pathogenic fungi is declining. Thus, the development of novel antifungal drugs is urgently needed. Secondary metabolites from marine organisms are plentiful resources with a range of chemical structures and bioactivities. Even though a number of substances with possible antifungal properties have been found, thorough evaluations that offer precise details regarding their underlying mechanisms are scarce. Marine animal antifungal compounds and their complex mechanisms of action target a variety of fungal cellular components, including the cell wall, cell membrane, mitochondria, chromosomes, drug efflux pumps, and certain biological processes, including vesicular trafficking, hyphal growth, and biofilm formation. This review is beneficial for

the future development of antifungal drugs since it summarizes the antifungal activity of secondary metabolites from marine species.

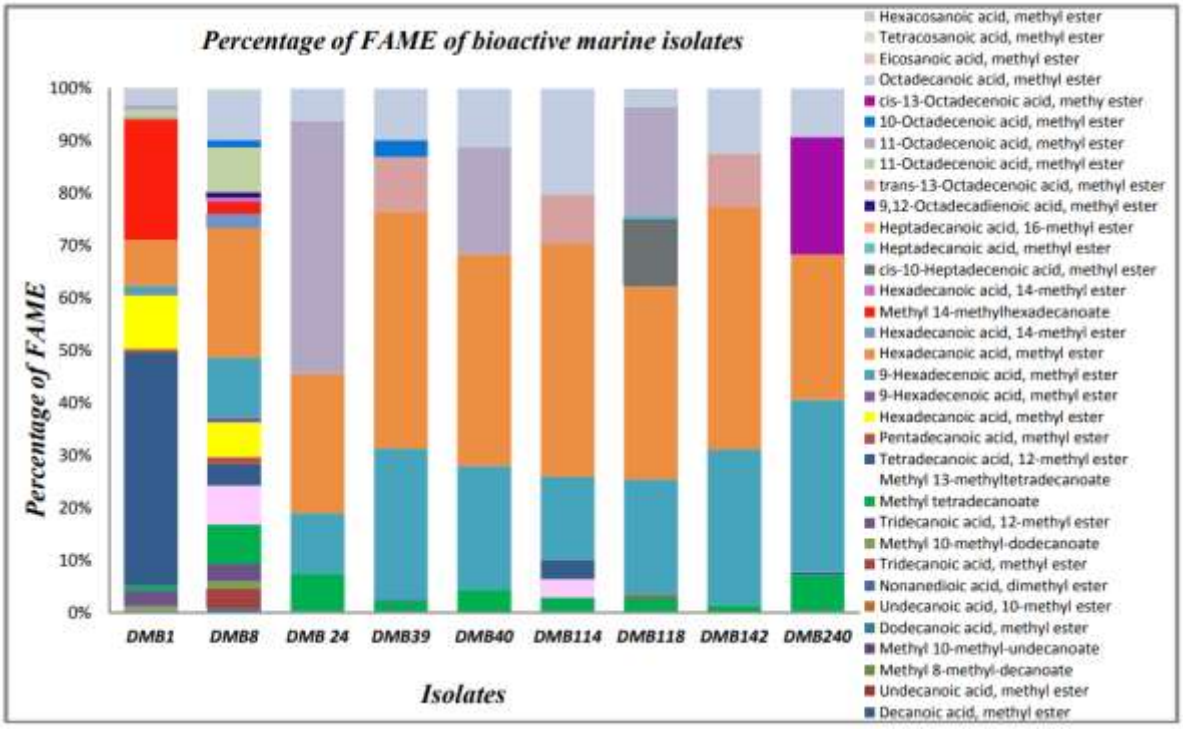

Figure 1: Comparative account of the composition and percentage

The identification of bioactive substances has benefited greatly from the use of marine environments. These ecosystems have been home to over 250,000 different types of life, ranging from microbes to invertebrates like sponges and ascidians. In the marine environment, the combination of temperature, salinity, and pressure has produced a variety of secondary metabolites that are absent on land. Numerous pharmacological characteristics, including antifungal activity, have been shown for these compounds obtained from marine sources. Furthermore, it has been demonstrated that chemicals derived from marine sources had favourable pharmacokinetic and pharmacodynamic characteristics, which could be the rationale behind their use in the treatment of drug-resistant IFDs. As a result, substances obtained from marine sources have great promise for creating novel antifungal drugs. Although numerous compounds with antifungal activity have been identified from marine sources, the mechanisms behind the antifungal action of most of these compounds remain unclear. The purpose of this review was to collect data on a variety of metabolites with unique antifungal actions that were obtained from marine sources [7].

The development of marine-derived antifungal medications is aided by this review. Fungal plasma membranes are essential for controlling cell shape and influencing a range of cellular processes, such as signal transduction, apoptosis, pathogenicity, cell recognition, and the stress response. Fungal cells are rich in lipids, including glycerophospholipids, sphingolipids, and sterols, particularly ergosterol. A practical antifungal strategy is to rupture the fungal cell membranes, as these are essential.

4. RESULT AND DISCUSSION

As a result, mitochondrial production is hindered, which exacerbates mitochondrial dysfunction and ultimately results in fungal cell death. One of the main causes of ROS buildup in the mitochondria, Complex III in Candida albicans, is inhibited by the respiratory chain inhibitor antimycin A. This lowers the growth of Candida albicans by raising oxidative pressure. For maximum virulence, pathogenic fungi rely on the glyoxylate cycle, which is found in mitochondria and consists of two processes catalysed by other enzymes as well as other reactions that are part of the tricarboxylic acid cycle (TCA). Three processes make up the TCA: aconitase converts citrate to isocitrate, citrate synthase converts oxaloacetate to citrate, and malate dehydrogenase catalyses the conversion of malate to oxaloacetate [14].

Isocitrate is subsequently hydrolysed into succinate and glyoxylate by one of the other enzymes, isocitrate lyase. Acetyl-CoA and glyoxylate are converted to malate by the second malate synthase[8]. One of the important glyoxylate cycle enzymes, isotrate lyase, is a crucial target. In mice with systemic candidiasis, a C. albicans mutant strain lacking isocitrate lyase shown a significant decrease in virulence and survival [12]. By disrupting respiratory chain Complex III and Complex, amidine aryl selectively affects yeast mitochondrial function, suggesting that fungal mitochondria would make a good target for antifungal drugs. The formation of biofilms occurs in four stages[15].

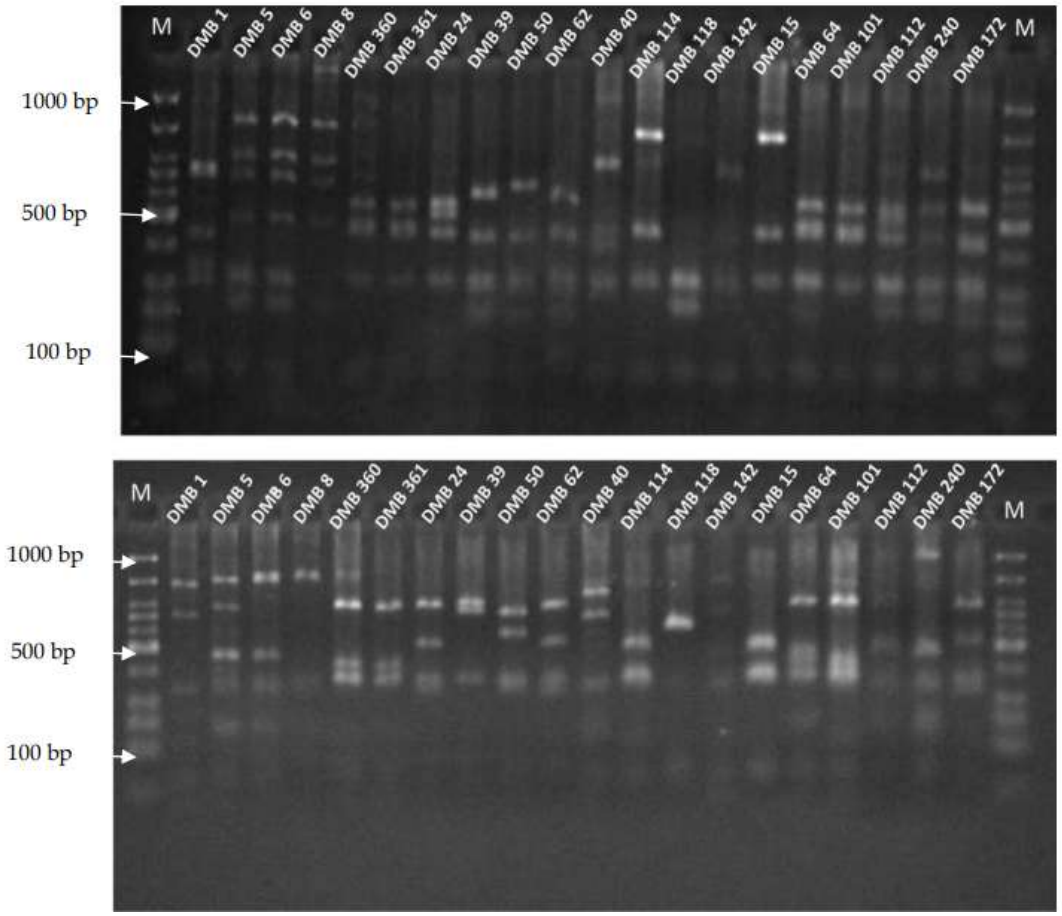

Figure 2: ARDRA analysis

The cells of albicans first adhere to the surface before first proliferating quickly. Then, as hypha form and fungal cells make EPS until they are completely enclosed, a process known as biofilm maturation. Quorum sensing, the basis of biofilms, facilitates microbial communication through signalling molecules, and adherent surface characteristics are among the factors that are known to obstruct biofilm formation. Lastly, the released dispersed biofilm releases C. albicans cells for additional growth and biofilm formation. A quorum-sensing substance called farnesol may prevent hyphal growth within the hyphal initiation mechanism. Because exogenous farnesol inhibits the formation of biofilms, it has an impact on cell adhesion, biofilm structure, and biofilm spread.

5. CONCLUSION

In summary, 96 compounds with promising antibacterial and antifungal properties that were derived from various marine species were found in this analysis. Since most of these compounds showed strong activities against antibiotic-resistant species of bacteria and fungi, such as methicillin-resistant Staphylococcus aureus, vancomycin-resistant bacteria, and many others, they hold great promise for the development of new antibiotic medicines that could address the issue of antibiotic resistance and reduce treatment failures in humans. Marine life, particularly bacteria and sponges, is the source of the majority of the novel antifungal and antibacterial medications presently undergoing clinical testing. The fact that so many chemicals in the oceans have not yet been identified suggests that the newly discovered compounds may only be the beginning, which is a very encouraging observation. It is possible to discover novel antifungals from marine creatures. A variety of antifungal activity and mechanisms of action are produced by this varied supply of secondary metabolites. More in vivo research is required to validate the antifungal activity of these intriguing active ingredients. In conclusion, using the secondary metabolites of marine species to treat IFDs shows promise.

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