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REVIEW ARTICLE

Advances, Fundamentals, and Machine Learning Contributions to Marine Microbial Antibiotic Synthesis

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ABSTRACT: Antibiotic resistance has become one of the most significant clinical crises of the modern day. With pathogens developing immunities against existing antibiotic medications, it has become essential to find alternative compounds that can inhibit the growth of these harmful bacteria. Microorganisms residing in marine environments are promising options for this purpose. This hypothesis is backed by previous experiments with the natural products of marine microbes, studies on their ecological roles and patterns of evolution, and advances in technologies for studying marine microbes. Diving deeper into this information, this paper highlights how breakthroughs in the field of marine-derived antibiotics—including *in situ* cultivation, CRISPR-Cas9 genetic engineering techniques, and numerous ML models such as Evodictor—have allowed researchers to access and study marine microbes' metabolites for antimicrobial properties with considerable success. We aim to establish that future drug discovery efforts should be shifted to our oceans, the 70 percent of our world that has been left largely unexplored.

KEYWORDS: Microbiology; Antimicrobials and Antibiotics; AI and Antimicrobial Properties; Antibiotic Synthesis; Marine Microbes..

Introduction

Since the discovery of penicillin by Alexander Flemming in the 1920s, pathogenic bacteria have developed various resistance mechanisms against antibiotic treatments. This results from the principle of "survival of the fittest", which applies to every species, from humans to bacterial pathogens. Infectious bacteria have responded to the presence of antibiotics and evolved to the point where existing antibiotics are rendered ineffective against many infections, creating a severe cause for concern in the healthcare community. For example, Flemming's penicillin and other common cephalosporins, such as methicillin, are no longer effective in treating *Staphylococcus aureus* infections, which continue to be one of the most common bacterial infections in humans. This ineffectiveness of antibiotics has led to a staggering increase in hospitalizations due to bacterial infections. A 2007 study by Klein *et al*. found that hospitalizations due to staph infections in the United States shot up from 127,036 in 1999 to 278,203 in 2005.[1]

Finding new sources of diverse antimicrobial compounds would pay dividends in diminishing this health crisis, and marine environments represent a reservoir of unexplored microorganisms that produce potent biosynthetic compounds with significant antimicrobial potential. This is mainly due to the vast biodiversity of the oceans, which are home to around four-fifths of the life on Earth. The array of life in the oceans is a strong indicator of diversity in the chemical structure of their biosynthetic compounds, which is crucial for discovering new compounds that can circumvent the resistance mechanisms that pathogenic bacteria have developed over the past century.

This review analyzes fundamentals and advances in antibiotic synthesis from marine microbes. Compiling information from over 100 academic papers, this review explores relevant innovations in genomics and biotechnology, reviews key concepts regarding marine microbial antibiotic synthesis, delves into machine learning applications to this topic, and discusses the practical implications and applications of the information in this review while addressing research gaps and strategies for overcoming them.

Discussion

This review is focused on following a systematic search strategy to interpret a wide array of marine microbial antibiotic synthesis studies. The search encompassed multiple scientific databases, including PubMed, SciHub, and ScienceDirect. The strategy employed involved the use of keywords such as "marine microbes", "antibiotic synthesis", and "genetic manipulation". The criteria for selection were focused on selecting peer-reviewed publications that gave insight into the methods, discoveries, or theoretical frameworks related to marine microbial antibiotic synthesis. Each article was screened by independent reviewers to assess relevance, methodology, and impact, ensuring an unbiased literature curation. Data from the selected studies were categorized according to specific themes related to advances and fundamentals in antibiotic synthesis, serving as the basis for in-depth analysis and discussion in the review.

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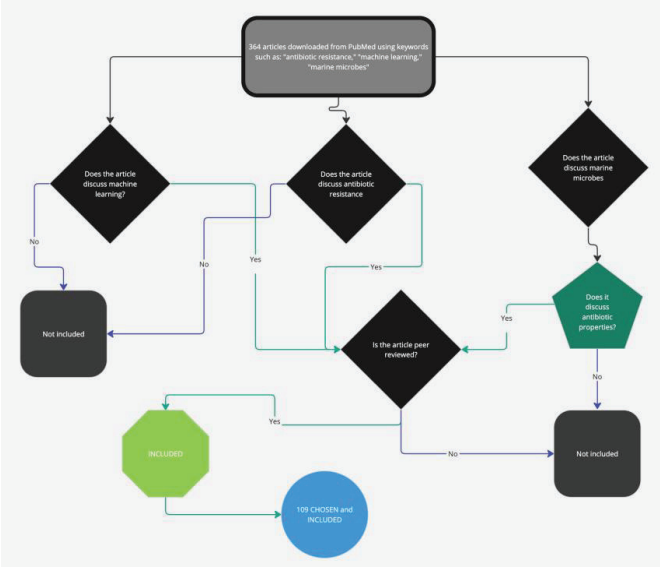

Figure 1: Flowchart depicting article selection process.

Advances in Marine Microbial Antibiotic Synthesis:

The development of antibiotic resistance has necessitated efforts to improve methods for cultivating bacteria, extracting their biosynthetic compounds, and analyzing inhibitory activity and potential against human pathogens. "Biosynthetic compounds" is a term that will be used frequently throughout the paper to refer to chemical compounds, such as metabolites, that are produced by living organisms. This section explores the topic of bacterial cell culture and delves into relevant strides in the fields of genomics and technology, maintaining a focus on marine microorganisms.

Culturable Marine Microbes:

The biodiversity of marine microbes and their clinical potential has catalyzed efforts to strengthen cultivation techniques further to investigate their applications to issues such as antibiotic resistance. Altering the source of nutrients in culture media based on the natural environments of different bacteria has been one approach. This idea is supported by the success of water-extracted matter (WEM), which has been used to isolate a variety of marine actinobacterial genotypes.[2] *In situ* cultivation translates literally to "in the original place," another promising innovation in cultivating marine microbes. The flagship technique of *in situ* cultivation is the diffusion chamber. This device allows agar matrices containing microbes to be placed in their natural environment, allowing exposure to growth factors while eliminating the risk of contamination.[3] Figure 2 depicts the dual-layer membrane setup integral to the diffusion chamber, which is crucial for maintaining the sterility of the culture while permitting the necessary nutrient flow. Although *in situ* cultivation is not flawless, the multitude of *in situ* techniques with various advantages and disadvantages provides researchers with a diverse toolkit that can be applied according to the nature of their studies.

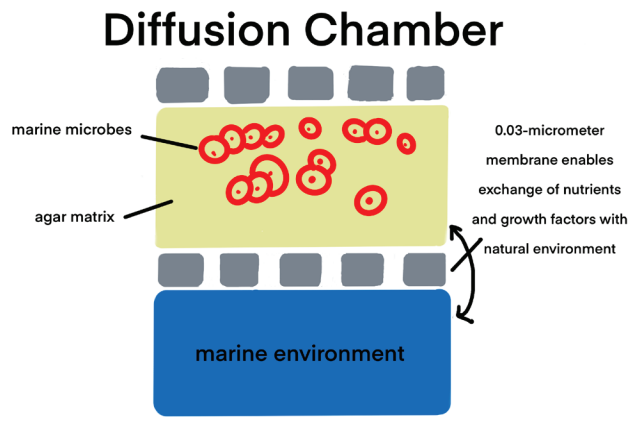

Figure 2: Dual-layer membrane setup for in situ cultivation experiment.[3]

In situ cultivation has been utilized in previous studies for bioprospecting culturable microbes. One study used a cryo-iP-late design, modeled after the iChip *in situ* technique, to cultivate Canadian Arctic bacteria.[4] Isolates were taxonomically identified with the 16S rRNA gene sequencing method and tested against relatives of ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.*) to identify antibacterial potential. They were subsequently exposed to the true ESKAPE pathogens to establish their clinical relevance.[5] *Pseudomonas prosekii* displayed the broadest inhibitory activity, proving effective against methicillin-resistant *S. aureus*, methicillin-susceptible *S. aureus, A. baumannii, E. faecium, and E. faecalis*.[5]

Newer *in situ* cultivation techniques can improve phylogenetic analyses of marine microbes. In a study involving the standard cultivation of *Rhopaloeides odorabile*, it was reported that 42 bacterial isolates were collected with phylogenetic connections to *Pseudonocardia* and *Gordonia*, among others. However, it was also estimated that these bacteria represented only around 0.1% of microbes present in the sponge.[6] Although marine microbes have been studied in the past, the lack of effective cultivation techniques has left the oceans as vast sources of bacteria and natural products with untapped potential. Applying *in situ* cultivation techniques such as diffusion chambers to phylogenetic analyses of marine microorganisms would likely increase the yield of bacterial isolates, which could be used in further studies on their biochemical diversity and antimicrobial activity.

Unculturable Marine Microbes:

These innovative techniques can be applied to the "great plate count anomaly," a phrase that refers to the challenge of culturing what has been labeled as "unculturable" marine microbes. Traditional cultivation methods, such as solid media cultivation and agar plate counting, typically recover less than 1% of the naturally occurring microbial density, a discrepancy attributed to the inability of those methods to replicate complex ecological interactions and the specific needs of each species.[5] Research has shown that innovative cultivation techniques—including co-culture systems, dilution-to-extinction methods, and diffusion chambers—can significantly increase

the cultivability of these microbes. Marine bacteria such as SAR11 clade, Woeseiaceae/JTB255, and bacteria from the phyla *Bacillota* and *Actinomycetota* are all notoriously difficult to cultivate; however, some studies have shown promising results over 1%, which alludes to the possibility of these marine microbes being culturable.

The advent of long-read metagenomic sequencing has radically changed the exploration of microbial diversity, particularly in accessing biosynthetic gene clusters (BGCs) from unculturable marine microbes. BGCs are groups of genes that drive the production of specific metabolites. Traditional short-read methods failed in assembling complete BGCs, a limitation overcome by long-read technologies. In a comprehensive study analyzing seawater from Aoshan Bay, Yellow Sea, China, 339 mainly full-length BGCs were recovered using long-read sequencing and genome mining. The analysis uncovered *Candidatus thermoplasmatota*, an uncultured archaeal phyla. Additionally, metatranscriptomic data revealed that about 30.1% of secondary metabolic genres within these BGCs were active, demonstrating their expression in environmental processes. Integrating long-read metagenomic sequencing with metatranscriptomic analysis offers a more precise and thorough way to uncover how BGCs function and how microbes adapt to their natural environments. In doing so, new avenues for compound discovery are opened by revealing the untapped potential of unique metabolite gene clusters.[6-8]

Recently discovered extracts from unculturable microbes have identified many antibiotics. This includes clovibactin, a novel antibiotic gained from uncultured soil bacteria, suggesting that this genre of reluctant-to-grow microbes can reasonably contribute to the antibiotic discovery pipeline. Clovibactin ligands interact through a hydrophobic interface to target the pyrophosphate of essential peptidoglycan precursors, including C55PP, Lipid II, and Lipid WTA. This event drives the irreversible sequestration of these precursors into supramolecular fibrils and is specific to bacterial membranes harboring lipid-anchored pyrophosphate groups. Such precision in target binding, coupled with the absence of resistance development, underscores the capacitating adaptations that uncultured bacteria possess for producing potent bioactive compounds. The discovery of clovibactin provides a case to point to unculturable bacteria as a rich reservoir for new antibiotics that will offer new mechanisms of action against ever-increasing resistance to existing infection treatments.[9-11]

CRISPR-Cas Systems:

In addition to cultivation techniques, genomic analyses and gene-editing systems have been studied for their potential applications to drug discovery research. Ribonucleoprotein complexes (RNPs) such as CRISPR-Cas9 and Cas12a have greatly advanced genome editing, allowing for targeted modifications such as gene disruptions, deletions, and point mutations in various organisms. Cas9 and Cas12a (Cpf1) from Streptococcus pyogenes are the workhorses of this technology, guided by guide RNAs (gRNAs) to specific DNA sequences to make cuts. These systems have been successfully used in *Streptomyces* spp., *Lactococcus lactis*, *Pseudomonas putida*, *Escherichia coli*, and other microorganisms with varying degrees of success and application, demonstrating the flexibility and potential of CRISPR in microbial engineering.[12, 13]

The CRISPR pathway targeting mechanism relies on PAM sequences, specific DNA motifs that Cas nucleases recognize. Mutations in these sequences among different organisms have led to the development of a broader, more unique range of PAM-compatible Cas, expanding the targeting capabilities of CRISPR programs. Base editing represents a leap forward in precision, using synthetic enzymes fused to inactive Cas9 or Cas9 nickase to modify single DNA bases without the double-stranded breaks. Prime editing extends such capabilities to a wide range of species. However, its integration into microbial antibiotic synthesis still requires improvements due to the components' sheer complexity. gRNAs have been engineered to be highly specific to improve accuracy and reduce unwanted variation. Truncating or chemically modifying gRNAs increases their binding specificity, reducing potential off-target effects by making sure that the gRNA accurately matches the DNA.[13]

Synthetic Biology and Metabolic Engineering:

The Streptomyces SUK 48 study sheds light on known drugs such as kanamycin and gentamycin and biosynthetic pathways ripe for investigation. Using metabolomic and genomic analyses, scientists can identify gene-specific methods of regulating antibiotic biosynthesis. This enables the improvement of known compounds and the discovery of entirely new antibiotics. By manipulating these groups of genes, researchers can develop antibiotics to combat resistant strains, expanding the arsenal against infectious diseases. Nonribosomal peptide synthetases (NRPS) are instrumental in synthesizing antibiotic compounds, especially those not created via the typical ribosomal pathway. These complex enzyme machines combine various building blocks, including obscure amino acids, to produce unique antibiotics. The Streptomyces SUK 48 study demonstrates this capability of NRPS gene clusters with tools such as antiSMASH. These tools can help visualize those clusters, predict their products, and modify them to create improved antibiotics. This precise tailoring is key to unlocking more effective and targeted drugs.[14-17]

Horizontal Gene Transfer and Expression System:

Horizontal Gene Transfer (HGT) is vital to expanding the biosynthetic repertoire for antibiotic synthesis. It allows the transfer of complex biosynthetic pathways from marine microbes to other, more tractable laboratory hosts. By employing HGT, researchers can harness the genetic blueprints of marine organisms to manipulate antibiotic pathways, especially in organisms like *E. coli*, potentially facilitating more straightforward modification.

However, HGT also plays a role in spreading antibiotic resistance, evidenced by the transfer of triazole resistance in *Aspergillus fumigatus*. Understanding the mechanisms of HGT in pathogenic fungi is vital for developing strategies to counteract the spread of resistance genes. Another technique to explore is codon optimization. Codon optimization is a technique that regulates the expression of marine microbial genes

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in heterologous hosts.[18, 19] As the name suggests, it modifies the codon usage of the gene of interest to align with the preferred codon usage of the host organism, thereby enhancing translation efficiency, protein folding, and expression levels. Synthetic biology complements these techniques by providing tools for fine-tuning gene expression. Synthetic promoters and ribosome binding sites (RBSs) can effectively control biosynthetic genes' expression levels, optimizing concentrations of enzymes to improve the yield and efficacy of newly produced antibiotic substances.[20, 21]

Innovative Screening Techniques:

Pioneering endeavors in unearthing new antibiotics primarily focus on groundbreaking techniques designed to awaken dormant or hidden metabolic routes within actinomycetes. Goadsporin, extracted from *Streptomyces* sp., proves adept at triggering both secondary metabolism and sporulation across a diverse array of *Streptomyces* variants. Diverging slightly, growing Streptomyces alongside bacteria rich in mycolic acid in a combined-culture process has been shown to catalyze positive improvements in almost 90% of Streptomyces variants studied.[22, 23] The wide-ranging suitability and potent effectiveness of these methodologies in spurring the production of secondary metabolites substantially amplifies the effectiveness of screening for naturally occurring compounds. Persisting refinements of these methods are anticipated to elevate both their accuracy and potency, steering the quest for novel antibiotic agents.[23]

Another interesting technological advancement comes with biosensors, devices that measure the presence of an analyte by binding with it through a specific biomolecular component. Continual enhancements in biosensor technology, with a deliberate emphasis on augmenting accuracy and operational efficiency, are indispensable for the exact identification of antibiotic traces in culinary products.[24] This technology could be applied to slow the development of antibiotic resistance by reducing the exposure of antibiotics to Enterococci bacteria that reside within the digestive tract. Additionally, the previously addressed *in situ* cultivation techniques such as iChip and advances in genomics and metabolomics allow experts to probe deeper into unexplored environments and quiescent genetic sequences—directly confronting the escalating antibiotic resistance crisis.[25] Current advancements in liquid chromatographic techniques have opened doors for meticulously scrutinizing an extensive array of antibiotics alongside beta-lactamase inhibitors, which was used in a study to screen 19 unique substances—a feat that far surpasses previous limits.[26]

Biotechnological Advances:

Biotechnology's applications in antibiotic research extend beyond innovations in screening techniques. The discovery of new antibiotics has shifted in recent years from giant pharmaceutical companies to smaller biotechnology groups, owing to changes in economic strategies and the pressing need to combat antibiotic resistance.[27] Advancements in this field are imperative in bringing newly discovered antimicrobial compounds to widespread commercial use.[28]

In their review article, Silber *et al*. outline potential applications for biotechnology in each of the four steps of drug development from marine fungi: discovery of compounds, production, downstream processing, and lead development. Controlled miniaturization is a particularly intriguing biotechnological advancement in the compound discovery phase, as discussed by Silber *et al*. Small-scale fermentation systems such as the BioLector microbioreactor use microtiter plates to evaluate large numbers of cultivation parameters simultaneously in an efficient and targeted manner. Considering that optimizing cultivation is a significant issue in extracting biosynthetic compounds from marine microbes, this is a prime example of how biotechnology can push the boundaries of marine-derived drug discovery.[29]

Bioinformatics, a subfield in biotechnology, also has well-established uses in antibiotic development. In their review, Gomes *et al*. covered the Basic Logical Alignment Search Tool (BLAST) applications. This bioinformatics search engine allows users to compare protein, amino acid, and nucleotide sequences against existing databases. With BLAST, researchers can use genetic information from microbes of interest to make accurate predictions regarding protein function based on known orthologs or genes from different species that retain similar functions. This valuable tool at the intersection of genomics and biotechnology could be used to narrow the search for marine microbes with promising biosynthetic compounds, thereby increasing the efficiency of drug discovery studies.[30]

Fundamentals of Marine Microbial Antibiotic Synthesis:

Antibiotics used today in clinical settings to treat bacterial infections are primarily produced by natural biological processes in microorganisms. Considering the gradual rise in antibiotic resistance mechanisms among pathogenic bacteria, it is crucial to understand how these processes evolved due to their ecological roles and how this evolution has contributed to the structural and chemical diversity of the natural products used in modern antibiotic treatments.

Biochemical Pathways:

Secondary metabolites are important compounds naturally produced by bacteria for various functions. Polyketides and nonribosomal peptides are subgroups of secondary metabolites that demonstrate potent antimicrobial activity due to their immense structural and chemical diversity. Polyketide synthases (PKSs) in marine microbes are responsible for the microorganism's biosynthesis of polyketides, and they can be divided into two main subgroups: multimodular (type I) and iterative (type II).[31] Although type I and II PKSs function similarly, they differ structurally. While multimodular PKSs can be described as mega enzymes with separate domains, iterative PKSs are split into multiple enzymes, each performing one function. Similarly to type I PKSs, nonribosomal peptide synthetases (NRPSs) are structured as large enzymes with different modules that assist in activating amino acid building blocks, elongating and modifying, and releasing the peptide.[32]

Marine microbes, in particular, have contributed to the discovery of around 70% of clinically relevant NRPs.[33] This

is mainly due to the extreme conditions exclusively found in marine environments—unusual temperatures, high pressures, low pH, and high salt concentration—which have forced the biochemical pathways of marine microbes to adapt, resulting in the diversity observed in their secondary metabolites today.[34] A considerable number of NRPs with antibacterial properties have been studied, such as Bogorol, derived from marine *Bacillus laterosporus*, displaying activity against MRSA and vancomycin-resistant *Enterococcus* spp.[33]

Ecological Perspectives:

Microorganisms produce the biosynthetic compounds discussed in the previous section primarily for competition in their natural environment. Non-transitive competition networks exemplify a type of competitive interaction between different microbes in which each strain can overcome or inhibit the growth of another through a variety of mechanisms and properties, often involving their natural products.[35] In specifically marine environments, large amounts of bacteria are concentrated on surfaces, forming intricate communities known as biofilms.[36] These densely packed biofilms increase competition among marine bacteria, eliciting the need for a diverse set of antimicrobial compounds as a tool for survival. Within these biofilms, biosynthetic compounds are also involved in quorum sensing (QS), which refers to cell-cell communication in which a synthase protein produces a chemical signal that can activate response regulators in other cells, depending on signal density.[36] This has given marine microbes another antimicrobial mechanism in quorum quenching (QQ)—disrupting QS signals between bacteria.[37] Marine microbes have shown the ability to produce quorum sensing inhibitors (QSIs) and extracellular QQ enzymes to disrupt the transmission and reception of QS autoinducer signals.[37-39] Regarding human bacterial infections, QS likely supports pathogenic virulence, giving QQ-equipped aquatic microorganisms unique weapons in their antibiotic toolkits that may prove useful in avoiding pathogenic bacteria's resistance mechanisms against more traditional drugs.

Historical and Evolutionary Insights:

Like the traits of all other organisms on Earth, marine microbes developed genes for the biosynthesis of secondary metabolites—known as biosynthetic gene clusters (BGCs)—over time, according to Darwinian evolutionary principles. Over time, as microbes are exposed to different environmental conditions and competitive species, the genes that code for their production of natural products mutate. This is exemplified by *Actinobacteria* spp., which possess the capacity to produce a range of natural products primarily because of their environmental interactions that have led to the evolution of different biosynthetic potentials.[40-46] The modular organization of PKSs and NRPSs discussed in the biochemical pathways section are notably susceptible to structural and functional changes—contributing to altered polyketide and nonribosomal peptide products due to genetic evolution.[47]

Despite the vast population of marine microbes still left unexplored for their secondary metabolites, there have been recent key discoveries of marine-based antibiotics. Macrolactin J, isolated from *Bacillus* spp., has shown activity against human pathogens *Bacillus subtilis* and *S. aureus*.[48] Emerixanthones, derived from *Emericella* sp. in the South China Sea, have proven antimicrobial activity against a majority of ESKAPE human pathogens, successfully inhibiting *E. coli*, *K. pneumoniae*, *E. faecalis*, *S. aureus*, and *A. baumannii*.[49, 50] A comprehensive table detailing information on the antimicrobial activity of additional compounds isolated from marine microbes is included below in Table 1. The promising results from these marine-derived antibiotics add further incentive to explore marine microbes as a viable source of antibiotics in the fight against antibiotic resistance.

Table 1: A table detailing the inhibitory activity of marine-derived biosynthetic compounds.[48-50]

Species (Strain)	Compound	Susceptible pathogens
Marinactinospora thermotolerans (SCSIO 00652)	Marthiapeptide A	*M. luteus, S. aureus, B. subtilis*
Streptomyces scopuliridis (SCSIO ZJ46)	Desotamide B	*S. aureus, S. pneumoniae*
Streptomyces droxdowiczii (SCSIO 10141)	Marfomycins A, B, E	*M. luteus*
Verrucosispora sp. (AB 18-032)	Abyssomicin C	*MRSA, VRSA*
Streptomyces niveus (SCSIO 3406)	Marfuraquinocins A, C, D	*S. aureus*
Streptomyces sp. (SCSIO 01127)	Lobophorin F	*S. aureus, E. faecalis*
Streptomyces sp. (12A35)	Lobophorin H	*B. subtilis*
Streptomyces sp. (NTK 937)	Caboxamycin	*B. subtilis, S. lentus, S. epidermidis*
Micromonospora sp. (RJA4480)	Sporalactams A, B	MRSA
Streptomyces sp. (LS298)	Quinomycin G	MRSE, MRSA, VRE
Streptomyces sp. (CA-271078)	Napyradiomycins	MRSA
Streptomyces sp. (ZZ338)	Actinomycins D, V, X0	MRSA
Penicillium sp. (KH1-22)	Peninaphones A-C	MRSA, VRE
Aspergillus sydowii (SP-1)	Acremolin C	MRSA, MRSE
Engyodontium album (LF069)	Engyodontochones A-F	MRSA
Streptomyces sp. (B475)	Quinomycin A	*E. coli*, ESKAPE (excluding *Enterobacter* spp.)
S. althioticus (MSM3)	Desertomycin G	*M. tuberculosis*, VRE, MRSA, *C. urealyticum*

Introduction to Machine Learning in Biomedical Research:

Machine learning (ML), an integral part of artificial intelligence, is revolutionizing biomedical research, especially antibiotic discovery. It uses algorithms to identify patterns and predict outcomes, aiding in drug design and treatment prediction. ML is increasingly important because of more powerful computers, data availability, and better software. Recent advances in ML have led to novel diagnostic and therapeutic modalities, emphasizing its important role in future medical advances.

Machine Learning Techniques and Applications:

In biomedical research, machine learning shows great potential in furthering the ability to understand complex diseases and improve patient care. Supervised learning uses labeled data to predict outcomes, such as categorizing tumors or forecasting patient responses to treatment.[51, 52] It has the unique ability to learn from vast amounts of the known to predict the unknown—including discrete and continuous outputs handled by classification and regression, respectively.

Unsupervised learning does not rely on predefined labels. Instead, it explores the data structure to unearth patterns or groupings, such as identifying genetic profiles. Techniques such as clustering and dimensionality reduction are vital here, used for parsing through complex datasets to find natural groupings or reduce the number of variables to the most relevant ones.[52] Unsupervised learning can be used to dissect metagenomic data from marine sediments, revealing patterns and clusters among microbial communities. For instance, it may identify a subgroup of *Pseudoalteromonas* bacteria with unique gene

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sequences suggesting unknown chemical structures that could lead to new antibiotic classes.

Deep learning, a subset of ML, takes that concept further with neural networks that mimic brain structure, processing layers of information to learn from data. These networks—specifically, artificial neural networks (ANNs) or convolutional neural networks (CNNs)—process layers of information to learn from data, such as medical images and sequences of genetic information.[52] Each layer consists of artificial neurons characterized by an activation function and a weight determining if and how information is passed to an ensuing neuron in the following layer, much like in a biological neuron.[52] CNNs can analyze molecular structures of known antibiotics and predict how modifications might enhance their effectiveness or reduce resistance. This can be applied to molecules derived from marine fungi, predicting alterations that might make an existing molecule a more potent and resilient antibiotic. Figure 3 represents an example of a deep neural network.

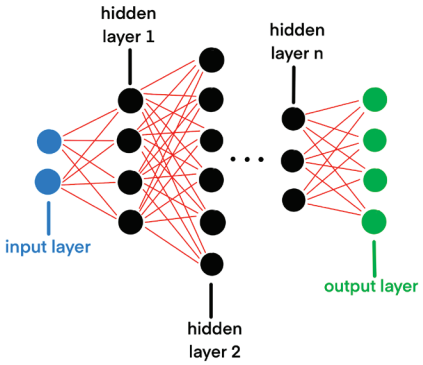

Figure 3: Depiction of the flow of information from the input layer to the output layer in a deep neural network.

Machine Learning in Culturing and Genomic Analysis:

Predictive models in culturing marine microbes have moved towards more complex environmental and genetic interactions to enhance antibiotic synthesis. Advanced techniques, such as those described by Avsec *et al.* in their study of gene expression prediction, utilize deep learning to integrate long-range genomic interactions, demonstrating how genes may behave in different environments.[53]

Deep-learning technology can predict gene expression responses to environmental factors such as temperature fluctuations and nutrient availability. Using the collected data, it is possible to tailor culturing conditions to maximize antibiotic yield. Enformer utilizes distal regulatory elements that impact gene activity, such as enhancers and repressors. In genomic data analysis and gene prediction, the technology has similar effects. The complexity of gene regulation comes with the many potential interacting loci spread across the genome. Enformer's ability to capture up to 100kb of long-range interactions is crucial for understanding regulatory mechanisms.

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Machine Learning in Metabolic Pathway Analysis:

Similarly, the new computational model Evodictor employs ML techniques to delve into the evolution of bacterial metabolic systems. Meticulously scanning over 3000 bacterial genomes, it anticipates shifts in gene acquisition and loss.[54,55] The framework's predictive modeling, keenly aimed at the intricate, long-term evolution at the system level, becomes particularly vital in metabolic systems where gene alterations are observed.[55] PiDeeL, a designed deep learning framework influenced by the details of metabolic pathway data, advances glioma survival scrutiny and pathological categorization.[56] The methodology elevates performance metrics, impacting oncological pathology prognostication and survival rate studies. The integration of HRMAS NMR spectroscopy accentuates PiDeeL's contribution to oncological therapy and the art of computational modeling within healthcare domains.[56] Evodictor, alongside PiDeeL, showcases groundbreaking strides in harnessing machines and deep learning for evolutionary biology and oncology. The integration of such technologies into antibiotic research shows the impact of ML in shaping the future of medical innovation.

Machine Learning in Screening and Identifying Novel Antibiotics:

AI is another powerful tool in discovering novel antibiotic medications because it can effectively determine whether a novel biosynthetic compound also has a novel mode of action by comparing it to large databases. This is important because it helps researchers quickly determine whether or not a new drug can avoid pathogens' existing resistance mechanisms.[57] The utilization of AI has catalyzed the emergence of halicin against MDR bacteria, which operates by disrupting the electrochemical gradients of bacteria and has proven efficient in preventing *E. coli* strains from developing resistance.[58] Scientists have found a novel antibiotic potent in its action against *Acinetobacter baumannii* utilizing ML techniques reliant on novel antibacterial properties.[59] These compounds—for example, halicin—that are discovered with the aid of AI often model activity against notorious human pathogens that are otherwise difficult to treat, such as ESKAPE pathogens Enterobacter sp. and A. baumannii.[60]

Novel models and intricate neural networks such as DNNs and RDKit have played a hand in finding new antibiotic agents while unraveling the complexities of bacterial resistance.[61, 62] ANNs, introduced in a previous section, are vital in finding the complexities of medical datasets, a process instrumental in unearthing new antibiotic candidates.[63, 64] Ligand-based QSAR models working with ANNs can identify several novel antibiotic properties. Additionally, ANNs trained on bond-based physiochemical (MOLMAP) molecular descriptors

could identify 84% of the activity of 19 compounds tested on *S. aureus*.[65, 66] Moreover, AI-fueled drug discovery, specifically focusing on antibiotics through high-throughput screening, drastically hastens the pinpointing of potential chemical entities.[67]

Data Integration and Multi-Omics Approaches:

In contrast to single-omics investigations, multi-omics strategies provide a deeper understanding of the intricate web of information that forms the backbone of disease dynamics. The capacity to scrutinize extensive datasets from numerous omics layers through the lens of AI algorithms could pave the way for antibiotic treatments that are not only more accurate but also markedly more efficacious.[68-70] These innovative methodologies enable a thorough exploration of Lactic Acid Bacteria (LAB), particularly within the convoluted environment of the gut's microbiome.[71-73] Progressive strides in multi-omics tools stand at the forefront of surmounting the barriers inherent in conventional investigative methods, paving the way for revelations about interactions of LAB and their prospective contributions to the realm of antibiotic development.[74]

Navigating through the dense and expansive omics data demands meticulous strategizing and custom-tailored statistical scrutiny. A regression-based method known as "mediation analysis" was created to integrate single nucleotide polymorphism (SNP) and gene expression data, with gene expression acting as the mediator for the causal pathway linking SNPs to disease.[75, 76] Variations of this process have been seen in other methods in other omic layers. At a pivotal juncture in this process stands the task of ID conversion, where it becomes essential to harmonize corresponding elements strewn across various omics strata. Accomplishing this feat requires employing resources like KEGG and other indispensable tools to ensure seamless data amalgamation for deciphering biological analyses, which allows for novel perspectives on the data.[77] Typically, multi-omics are collected on a control set of samples; however, when this is not the case, models will typically infer genetic signatures (eQTL) or phenotypes based on genotypes.[78, 79] The Genome-wide association studies (GWASs) enhance the detection of genetic variants in genome-wide association studies, especially with limited sample sizes. This approach is validated by analyzing genetic factors linked to triglycerides, BMI, and systolic blood pressure, improving statistical power in GWASs under specific conditions and steered by mechanisms related to translation regulation and protein degradation rates.[80-87]

Another approach utilized multi-omics to prioritize *Klebsiella pneumoniae* as potential drug targets. Essential to this endeavor is the ability to pinpoint revolutionary drug targets, a testament to the capacity for surmounting the challenges posed by antibiotic resistance.[88-90] In the field of antibiotic resistance, systems biology offers crucial insights, especially in the context of antimicrobial resistance (AMR). When used with AI, systems biology enables the identification of new therapeutic targets and strategies to combat antibiotic resistance.[91] The future direction in this field points towards a more personalized approach to disease treatment, leveraging the power of AI to analyze omics data, which could impact antibiotic development and the broader field of medical research.

Challenges and Considerations in Applying Machine Learning:

Previous sections have discussed the numerous advantages of machine learning and artificial intelligence in drug discovery. However, hurdles persist—namely, the scarcity and subpar quality of data, which impacts the precision of outcomes. Nevertheless, it remains crucial to acknowledge that AI, despite its prowess, cannot supplant the ingenuity of human scientists; instead, it should be harmoniously amalgamated with conventional approaches to significantly augment the drug discovery process.[92] Additionally, diverse local methodologies and patient characteristics frequently lead AI models to deliver subpar performances. It has become imperative to concentrate on bespoke applications, meticulously adapting algorithms to suit distinct environments. Central to this strategy is a commitment to precision-driven crafting and persistent education to refine these models to thrive in varied healthcare landscapes.[93]

Case Studies and Success Stories:

As previously mentioned, a team at MIT unearthed a revolutionary antibiotic called halicin by utilizing an innovative machine-learning technique. The AI-guided method adeptly sifted through over one hundred million chemical entities, pinpointing halicin—explored initially as a remedy for diabetes—owing to its formidable antibacterial prowess. Astonishingly, halicin confronts various bacterial adversaries, some of which have previously shrugged off all known antibiotic assaults. In trials involving rodents, halicin demonstrated its potential, hinting at a beacon of hope amidst the growing shadow of antibiotic resistance.[58] Researchers at McMaster University have harnessed the power of artificial intelligence, unlocking pathways to a plausible remedy for the formidable *Acinetobacter baumannii*, a superbug notorious for its resistance to existing antibiotics. These revelations mark a formidable leap in the realm of avant-garde advancements and creative breakthroughs within medical inquiry, underscoring the potency of AI in refining precision and efficacy in combating resilient microbial foes.[94]

Future Directions and Potential:

Marine microbial antibiotic discovery is witnessing a push toward the fusion of cutting-edge ML, biotechnology, and genomics methods. This strategy promises deeper dives into the ocean's biological riches, employing advanced genomic tactics to unearth unprecedented biosynthetic gene clusters. Expectations are high for ML algorithms, which are anticipated to escalate their proficiency in forecasting antibiotic potency and resistance patterns. Concurrently, CRISPR-Cas systems are on the brink of revolutionizing microbial genome manipulation, aiming to boost antibiotic yields significantly. The field of personalized medicine is also on the cusp of a breakthrough, with AI and omics data poised to play a significant role in crafting bespoke antibiotic treatments. Research efforts are progressively turning towards unique marine environments like coral reefs,

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seeking novel antimicrobial agents. These strides, which marry technology with a profound grasp of marine microbial ecology, are brimming with potential. They confront the challenge of antibiotic resistance and pave the way for innovative antimicrobial therapies.

Thematic Analysis of Literature:

After delving into the technical concepts behind the production of antimicrobial compounds in marine microorganisms and exploring advances in the scientific and technological communities aimed at improving techniques to identify these compounds, this section shifts towards a more streamlined focus on previous discoveries in marine antibiotics and potential geographical hotspots to be explored in the future.

Classification by Antibiotic Types:

Over the last century, the scientific community has discovered many different antibiotics with a broad spectrum of uses and functions. They have been divided into distinct classes to optimize the general understanding of these antibiotics and their functional mechanisms. Notable classes include aminoglycosides, tetracyclines, macrolides, sulfonamides, oxazolidinones, glycopeptides, and fluoroquinolones.[95] Focusing on specifically marine environments, macrolides, fluoroquinolones, and sulfonamides are prevalent in various aquatic conditions—mainly due to hydrophilic properties, biodegradation resistance, or large production volumes.[96]

The structural and chemical diversity between these antibiotic classes dictates their functional mechanisms. These mechanisms can be separated as either bacteriostatic or bactericidal antibiotics. These groups are described as either inhibiting bacterial growth or directly eliminating bacteria, respectively—although neither group has significantly more success in clinical applications than the other.[97] Macrolides, consisting of a lactone ring and attached deoxy sugars, are bacteriostatic antibiotics that block protein synthesis by binding to ribosomal subunits and disrupting the role of peptidyltransferase in the translation process.[98] Considering this information, it follows that the potent antimicrobial activity of macrolides can be attributed to their functional mechanism applicable to a biological process consistent amongst almost all bacteria. Similarly, sulfonamides are bacteriostatic in their function; their free amino and sulfonamide groups allow them to prevent bacterial folic acid synthesis, which is essential for protein and nucleic acid synthesis.[99,100] Fluoroquinolones, however, are bactericidal, as they target the vital DNA gyrase and topoisomerase enzymes by trapping them onto bacterial DNA strands, significantly damaging the DNA structure.[101] This apparent functional diversity between different marine antibiotic classes is helpful in prescribing effective antibiotic treatments based on the various resistance mechanisms that pathogens may present with.

Microbial Taxonomy and Antibiotic Production:

Among the sea of emerging marine antibiotic producers, it is important to recognize the marine microbes that possess proven inhibitory potential against human pathogens and their developing resistance mechanisms. The *Streptomyces* genus of *Actinobacteria* is particularly relevant in clinical settings for developing antibiotic treatments and has already been used against various pathogens. Chloramphenicol, synthesized from a natural product of *Streptomyces venezuelae*, has demonstrated activity against the notable ESKAPE pathogen *Staphylococcus aureus*.[102] Marine microbes have also been used in antibiotic discovery efforts to combat antibiotic-resistant pathogens—daptomycin is produced by *Streptomyces roseoporus*. It effectively inhibits strains of *Staphylococcus aureus* that have developed resistance to methicillin and vancomycin.[102,103]

The *Enterococcus* genus includes *E. faecalis*, one of the ESKAPE pathogens. Therefore, Enterococci bacteria's prolific production of bacteriocins—natural products that inhibit the growth of closely related strains—make them an intriguing option for synthesizing novel antibiotics to fight against antibiotic-resistant pathogens.[103] Due to the properties of bacteriocins mentioned above, enterocins (Enterococcal bacteriocins) possess inhibitory activity against Enterococci—including, most notably, *E. faecalis*.[104] Due to their role in natural microbial interactions, bacteriocins likely evolve along with pathogens' resistance mechanisms and, therefore, represent a potent tool to be explored in the coming years.

While polyketides and nonribosomal peptides are recognized as the most prominent secondary metabolites for clinical applications, siderophores are another important biosynthetic compound for antibiotic treatments. Iron is necessary for essential growth and living functions of pathogenic bacterial cells, and the high affinity for ferric iron that characterizes siderophores allows them to essentially steal any iron in the environment that the pathogens could use for development.[105] The importance of siderophores and their iron-chelating properties is especially pronounced in marine environments, where iron is essential for life but in low concentrations.[105] Pseudonochelin, produced by a species of *Pseudonocardia bacteria*, is a siderophore that has demonstrated antimicrobial activity against notable pathogens, including *E. coli, S. aureus, P. aeruginosa*, and *A. baumannii*, establishing the potential for siderophores to be utilized more frequently in antibiotic research.[106]

Environmental and Geographical Influence:

Environmental biodiversity's impact on antimicrobial drug discovery has been touched on sporadically throughout this literature review. Biodiversity is crucial in environments for drug discovery efforts because antibacterial treatments are derived from the natural products of different microorganisms. Increased biodiversity exposes organisms in a given environment to a broader variety of life. Therefore, their natural products would have evolved significantly to adapt to the diverse environment. Marine environments satisfy this condition, making them optimal for scientific study.

Within the oceans, coral reefs have emerged as specific hotspots for drug discovery, mainly because they hold 25% of marine biodiversity despite covering only around 0.2% of the ocean floor.[107] The Coral Triangle, located in the Pacific Ocean near islands such as Indonesia and the Philippines, houses coral species that represent around 76% of the known coral species

in the world and is, therefore, known as the most diverse coral environment in the world.[108] Within the coral triangle, areas such as the Visayan Sea and the South China Sea—highlighted below in Figure 4—have emerged as hotspots for bacteria with broad antibacterial activity against relevant human pathogens. For example, a study on Streptomyces species isolated from the Visayan Sea demonstrated their successful inhibitory activity against ESKAPE pathogens, with one isolate closely resembling *Streptomyces cacaoi* even displaying antimicrobial activity against all six ESKAPE pathogens.[109, 110]

Figure 4: Areas surrounding the Coral Triangle (red), such as the South China Sea (dark blue) and the Visayan Sea (light blue), have been established as geographical hotspots for natural product discovery.

Discussion:

Modern advances in marine microbial antibiotic synthesis are interwoven with our understanding of microbial ecology and genetics. Techniques like CRISPR-Cas systems and advanced culturing methods extend from a deep understanding of microbial life and its environmental interactions. The role of ML in enhancing genomic analysis and bioprospecting marks a significant development, enabling precise identification of biosynthetic gene clusters and more accurate predictions of antibiotic efficacy. Such key improvements in the scientific community's approach to marine-derived drug discovery are significant because they are beginning to unlock our world's vast marine microbial environments and the immense biodiversity that comes with them. Understanding how to isolate biosynthetic compounds from these unique marine microbes effectively has the potential to give researchers access to innumerable new antibiotic medications, possibly creating the opportunity to recreate the efficacy that antibiotics had when they were first discovered in the 1920s. Despite these advances, the complexity and diversity of marine ecosystems present ongoing challenges, necessitating refined methodologies to harness this potential fully and sustainably.

Transitioning marine-derived antibiotics from discovery to clinical use is complex and involves significant challenges in production scalability, regulatory approval, and market viability. Biotechnological advancements are critical in addressing these hurdles and providing tools for efficiently synthesizing and optimizing these compounds. A strategic approach, balancing innovation with sustainable resource use, is crucial in realizing the therapeutic potential of these marine discoveries.

Significant gaps remain in our understanding of marine microbial communities and their potential for novel antibiotic production. Many marine microbes are unculturable with existing methods, obscuring a substantial portion of microbial diversity and their bioactive compounds. Addressing this gap requires integrated efforts in genomics, computational biology, and culturing innovations to uncover and utilize this untapped diversity. Future directions must include sustainable exploration strategies, advanced genetic tools for microbial manipulation, and interdisciplinary research frameworks. Tackling these challenges is imperative for advancing the field of antibiotics and combating the growing threat of resistance.

■ Conclusion

In summary, this review on marine microbial antibiotic synthesis emphasizes the potential of marine microbes, along with ML and genomic technologies, in addressing antibiotic resistance. Despite progress, challenges such as sustainable exploitation, clinical translation, and the inaccessibility of many microbes persist. Future efforts should focus on sustainable exploration, advanced genetic manipulation, and interdisciplinary research to fully harness marine microbial diversity for developing new antibiotics. This approach is crucial in combating the growing threat of antibiotic resistance.

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