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Exploring Marine Bacterial Secondary Metabolites: Rich Reservoirs of Exceptional and Potent Antimicrobial Agents

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ABSTRACT

Marine natural products (MNPs) showcase a broad spectrum of significant bioactivities, spanning anticancer, antibiotic, anti-inflammatory and antiviral properties. In addition to marine microbes like algae, sponges, marine fungi and bacteria, in particular, has demonstrated the capacity to generate innovative secondary metabolites (SMs) characterized by unique and distinct chemical structural diversity. These unique compounds represent significant candidates for the advancement of new drugs or drug leads. Numerous studies have highlighted the importance of marine microbial secondary metabolites, with many possessing significant pharmacological activity. These compounds hold great promise in the development of potent antimicrobial drugs aimed at addressing infections caused by drug-resistant pathogens. Despite being relatively underexplored, marine organisms are now experiencing advancements in sampling techniques, genomic data availability, molecular biology methodologies, synthetic organic chemistry progress, and computational tools, with artificial intelligence. These developments are enhancing our ability to study and harness the potential of marine life for various applications. This review examines the landscape of these compounds, and their potential applications in combating microbial infections and highlights the contemporary techniques for screening marine drugs.

Keywords: marine natural products; secondary metabolites; marine bacteria; marine fungi; structural diversity; biological activity

1. INTRODUCTION

The world's oceans harbor an immense biodiversity of organisms thriving in vast diversity of environments, relying on diverse bioactive compounds for their survival. In this context, we explore how this wealth of marine life can be leveraged to discover bioactive compounds with potential pharmaceutical applications. The variety of life forms and pharmacological potential of molecules sourced from the marine ecosystems surpass those molecules which are derived from terrestrial sources [1]. Bioactive compounds derived from marine fungi, actinomycetes and bacteria and are increasingly capturing the interest of researchers. Progress in marine natural product development, along with advancements in marine and human genomics, is paving the way for improved personalized medicine and precision biomolecular therapeutics. The aim is to identify bioactive compounds that can produce marine biopharmaceuticals with greater potency, enhanced efficacy, and less side effects [2]. Marine biopharmaceuticals have the potential to address the subtle yet significant challenges of growing global concern, such as the rise in antibiotic resistance [3]. In worldwide, cancer is considered one of the most lethal diseases underscores the urgent need for developing new therapeutic agents with unique modes of

action. Consequently, significant research has been conducted to discover new cytotoxic drugs from natural resources, particularly marine organisms, microbes and plants [4]. Several molecules sourced from marine environments have demonstrated significant benefits in combating cancer. They achieve this by either inhibiting the growth of cancer cells or inducing apoptosis in human cancer cell lines. Advancements in organic synthesis, structural analysis, and bioactivity assessment have been instrumental in isolating and clinically evaluating numerous new anticancer agents [5,6]. The marine ecosystem is not only fruitful for discovering novel compounds but also serves as a resource for identifying new cellular targets for therapeutic interventions. Nearly five decades have passed since Bergman isolated spongouridine and spongothymidine from the marine sponge Tethya crypta. This discovery eventually led to the development of Ara-C (cytarabine, an antileukemia agent) and Ara-A (vidarabine, an antiviral agent), which were approved by the United States Food and Drug Administration (US-FDA) in 1969 and 1976, respectively [7]. It was also anticipated that compounds of marine origin can be accepted by humans with nominal manipulation. These secondary metabolites that are not needed by the organism for their primary metabolic processes, are purported to deliberate some evolutionary advantage [8]. Despite significant advancements in chemical synthesis and engineered biosynthesis of antimicrobial agents, nature still stands as the richest and most versatile reservoir for uncovering novel antimicrobial compounds Researchers worldwide are meticulously searching for novel sources of effective compounds with unique antimicrobial characteristics. They recognize the fundamental health risks posed by pathogenic organisms and are exploring marine microbial-derived natural products as a valuable contribution to combating microbial infections [9]. Contemporary techniques for screening marine drugs involve a combination of advanced technologies and methodologies aimed at efficiently identifying bioactive compounds from marine organisms. These techniques hold great promise for addressing unmet medical needs and advancing drug development in various therapeutic areas.

2.The Marine Environment: A Bounty of Prospects for Investigating Natural Products

The ocean is a central part of the biosphere on earth. It covers approximately 70% of the Earth's surface and plays a fundamental role in the absorption of the building blocks of life, such as nitrogen, carbon, oxygen, and sulfur. The ocean also plays an important role in controlling the climate erection [10,11]. The marine ecosystem consists of three interconnected processes. First, the physico-chemical system establishes fundamental niches, such as the water column and substratum, which are subsequently colonized by organisms. Second, these organisms engage in various interactions, including predator-prey dynamics, feeding relationships, competition, and mutualism. Third, the resulting ecology forms feedback loops that can modify the physico-chemical system, completing the cycle [12]. We are currently experiencing a new era of drug development, centered on natural products obtained from both marine and terrestrial sources [9]. Herein, a forthright but imperative question is “that why marine natural products (MNPs) are gaining the significant attention from researchers?” To answer this question, scientists are anticipated by studying the imperative physicochemical properties, structural characteristics, and drug potential of marine natural products and terrestrial natural products (TNPs) have been analyzed, highlighting their evolutionary differences. Specifically, we examine their distinct features from the standpoint of unique molecular fragments. Natural Products derived from marine origin usually possess extra-long chains and larger rings and MNPs also have more number of nitrogen atoms and halogens,

Table 1: A perspective of pipeline of marine drugs

Compound	Source	Activity	Status

Brentuximab vedotin	Mollusk	Anticancer	FDA approved
Eribulin mesylate	Sponge	Anticancer	FDA approved
Vidarabine	Sponge	Antiviral	FDA approved
Ziconotide	Cone snail	Chronic pain	FDA approved
Trabectedin	Tunicate	Anticancer	FDA approved
Cytarabine	Sponge	Anticancer	FDA approved
Plinabulin	Fungus	Anticancer	Phase III
Tasidotin	Bacterium	Anticancer	Phase II
Marizomib	Bacterium	Anticancer	Phase I
Arenamides A and B	Bacterium	Inflammation	Phase I

suggesting that MNPs may be produced by more unique biosynthetic pathways than TNPs. Researchers believe that natural products derived from marine sources with novel drug-like gallows have great potential to be drug leads or drug candidates in drug discovery progressions [13, 14]. Table 1 presents a selection of marine-derived drugs that have been approved by the Food and Drug Administration (FDA), along with several marine drugs currently in various phases of clinical trials [15].

3.Marine Microorganisms

The marine ecosystem comprises of number of species, many of which have no terrestrial equivalents. In recent decades, the concept of microbial communities in the marine environment has gained significant importance. This is due to the abundance and diversity of marine organisms and the crucial role of the marine microbiome in shaping the structure and function of oceans. Marine microbial secondary metabolites, known for their chemical diversity and varied bioactivities, are increasingly being applied in pharmaceutical research [16]. Marine microorganisms thrive in extreme habitats, leading to the development of unique physiological and metabolic capabilities not found in their terrestrial counterparts. The number of bioactive metabolites derived from marine microorganisms has reportedly increased exponentially. These microbes are now seen as an increasingly vital source of bioactive compounds with the potential to develop novel, high-value biopharmaceuticals, addressing the current shortage of innovative therapeutic agents [17,18]. Moreover, given that the biochemical reactions of marine microorganisms are influenced by their distinct growth environments, it is reasonable to infer that marine secondary metabolites are significantly diverse and unique [19]. Bioactive compounds produced by marine associated microbes are still largely unexplored. Therefore, the research over marine microbial-derived compounds for therapeutic purposes has colossal prospective for new discoveries. The growing demands for new antimicrobial and antitumor agents require to resistor the emerging diseases [18,20]. Developments in microbial culture techniques and diving expeditions have largely directed the drug discovery program towards the oceans. The identification of putative gene clusters in symbionts and free-living bacteria has confirmed the role of the marine microbiome as a producer of bioactive metabolites with potential applications in cancer treatment and combating microbial infections. Advances in microbiology, particularly in microbial cultivation techniques, have made many more producers

accessible for drug production. Additionally, genetic technologies and biochemical knowledge enable the large-scale derivatization of both new and existing natural compounds, optimizing them for therapeutic applications [20, 21]. Currently, we have a significantly expanded arsenal for discovering new drugs from marine microorganisms (Fig. 1).

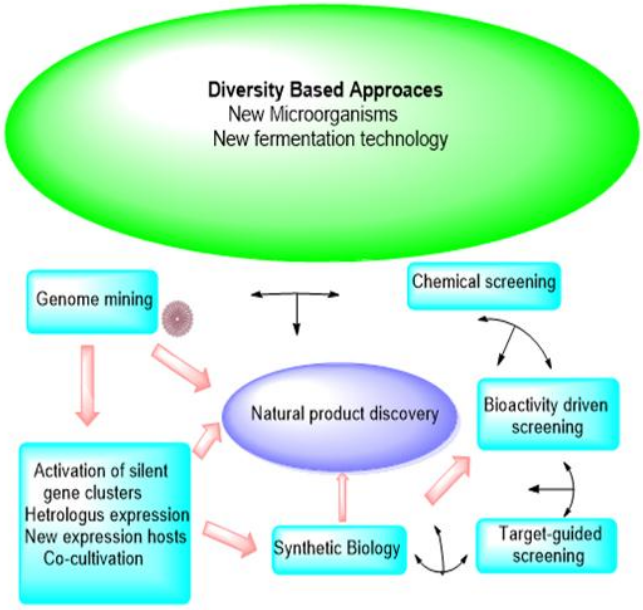

Figure 1: Multidisciplinary cooperation for natural product discovery from marine microorganisms

4.Marine Bioactive Natural Products from Microorganisms

Microbiology has emerged as a remarkable field of science in topical decades, with microbes being utilized across various stages. For over fifty years, soil microbiota has been the focus of extensive investigation worldwide. This focus may be attributed to the relative ease of isolating microbes from the lithosphere compared to other domains of the Earth. The discovery of penicillin from *Penicillium notatum* by Alexander Fleming in 1928 marked a significant shift from plants to microorganisms as sources of natural products. Since then, compounds derived from microorganisms have been widely used in medicine, the food industry, agriculture, and scientific research [22]. This trend is now shifting as the development of novel drug agents has slowed, and many chemical formulations derived from terrestrial microbes appear repetitive and costly. The first marine antibiotic, pentabromopseudilin, was described over five decades ago [23], Marine microorganisms are now believed to be the largest source of novel drugs. Their biochemical diversity, along with their ability to produce inimitable secondary metabolites with antimicrobial, antiglioma and nutritive effects, has focused their pervasive use in the monetary and industrialized production of drugs [24]. The marine microbiota is a promising and virtually limitless source for new drug development, particularly for novel antibiotics to combat diseases and drug-resistant pathogens, which pose a significant threat to public health. To date, more than 30 compounds are in clinical or preclinical trials. Currently, 16 out of 20 marine-derived anticancer compounds under clinical trials originate from microbial sources. Examples include didemnin B (Aplidine™) and thiocoraline, both used in treating various cancers. Notably, anticancer activity appears to be a primary focus, as indicated in Figure 2. However, this does not imply that cytotoxic activity is the predominant bioactivity of marine

natural products (MNPs). The bioactivity of MNPs is often influenced by a variety of factors. For a long time, significant amounts of scientific research funding have been directed toward anticancer drug development [25,26].

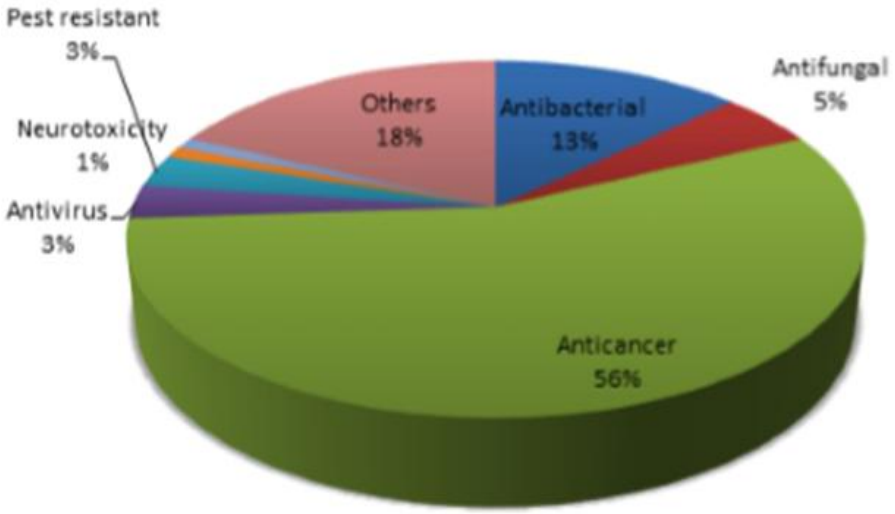

Figure 2: Percentage distributions of bioactive marine natural products

Major classes of microbes such as marine bacteria, actinomycetes, and fungi hold top positions in the hierarchy of all organisms, given their role in producing a diverse array of bioactive secondary metabolites with impending pharmacological applications. Despite this, there are numerous logistical challenges that need to be addressed before large-scale bioprospecting of marine microorganisms can become a reality. Unique novel secondary metabolites with properties such as antitumor, antiviral, antifungal, antioxidant, and anti-inflammatory effects have been extracted and identified from marine microorganisms. These compounds hold promise for drug discovery after undergoing clinical trials [27,28]. Figure 3 shows different bioactive marine natural products have been isolated from marine microorganisms. Indeed, symbiotic microbial consortia are also emerging as a source of bioactive molecules with pharmaceutical potential. Bacteria and fungi sampled from various sources such as the surfaces of marine plants, deep-sea sediments, and the inner tissues of invertebrates are increasingly capturing attention in this regard [29,30].

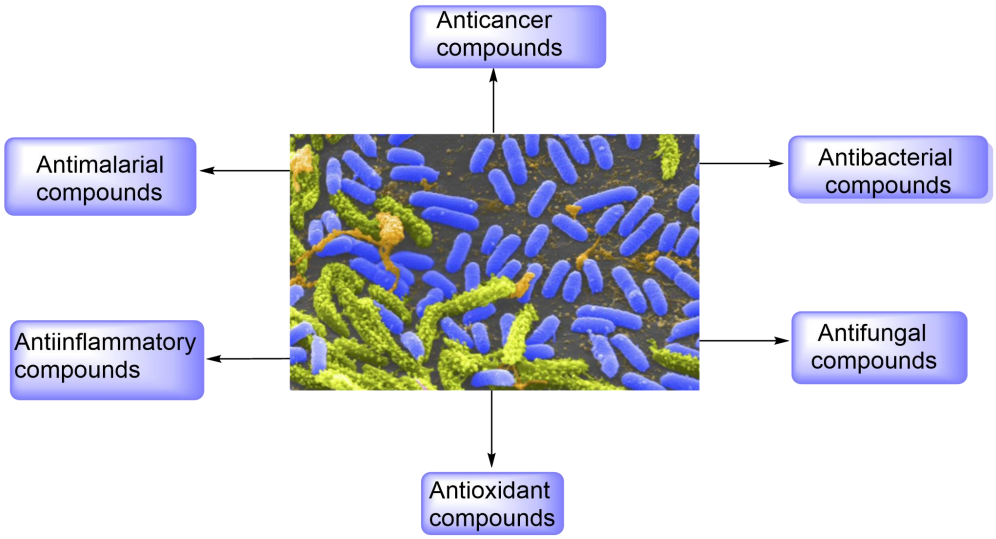

Figure 3: Different bioactive marine natural products from marine microorganisms

5.Bioactive Secondary Metabolite from Marine Bacteria

Marine bacteria, particularly marine actinomycetes, stand out as vital contributors to the search for novel bioactive compounds, making them significant reservoirs for both established and emerging drugs [31]. In 2008, the initial findings regarding the antimicrobial properties of Stenotrophomonas strains sequestered from deep-sea invertebrates emerged. It was noted that six Stenotrophomonas strains obtained from ophiura, sponge, sea urchin and samples exhibited noteworthy antifungal capabilities. These strains demonstrated significant inhibition of Gram-positive microorganisms [32]. Bacillus species are commonly discovered in marine mud and sediments, yet they can also be found in association with marine benthic organisms. These marine Bacillus strains have the capability to generate peptide compounds that exhibit antimicrobial properties [33]. The antimicrobials derived from the marine bacteria belong to the class of terpenoids, lactone, phenol, peptides, sterol, phthalate, fatty acid, steroidal glycoside cyclic polysulphide, polysaccharide, glycoproteins glycerol derivate, etc. Their molecular targets are bacterial membranes and intracellular molecules like protein, RNA and DNA [34,35]. Table 2 shows the marine peptides that derived from bacteria have biopharmaceutical potential [36].

Table 2: Marine peptides that derived from bacteria have Pharmaceutical potential

Source	Activity	Inhibition
Bacillus mojavensis	Antifungal	Phytopathogenic fungi
Streptomyces sp.	Antibacterial	*Enterococcus faecalis*
Photobacterium sp.	Antibacterial	*Staphylococcus areus*
Photobacterium sp.	Antibacterial	*Escherichia coli*

6.Bioactive Secondary Metabolite from Marine Actinomycetes

Actinomycetes stand out as incredibly significant prokaryotes in both biotechnology and economics. Among the notable genera of actinomycetes are Streptomyces, Arthrobacter, Actinomyces,

Corynebacterium, Micromonospora, Micrococcus, and numerous others. The secondary metabolites synthesized by actinomycetes showcase a diverse array of bioactivities [37]. Secondary metabolites with potent antimicrobial properties are extensively utilized as powerful antibiotics, effectively combating infections. Consequently, pharmaceutical manufacturing dominates the exploitation of antibiotic-producing actinomycetes. Marine actinomycetes within the Micro monosporaceae family exhibit remarkable prowess as producers, leading the forefront in this field [38]. Chartreusin, initially discovered by Leach et al. from *Streptomyces chartreusis*, demonstrates not only antibacterial properties but also exhibits significant antitumor activity against various human cell lines [39]. Table 3 shows some macrolide polyenes with antifungal activity derived from Streptomyces species. Table 4 shows some antibacterial compounds isolated from actinomycetes.

Table 1: Antifungal agents derived from *Streptomyces* tend to be macrolide polyenes

Antifungal Compounds	Source	Reference
Nystatin	*Streptomyces noursei*	[40]
Amphotericin B	*Streptomyces nodosus*	[41]
Urauchimycins	*Streptomyces* sp.	[42]
Antimycin	*Streptomyces* sp.	[43]
Chandrananimycins	*Actinomadura* sp.	[44]
Natamycin	*Streptomyces natalensis*	[45]

Table 2: Antibacterial compounds isolated from actinomycetes

Antibacterial Compounds	Source	Reference
Chandrananimycins	*Actinomadura* sp.	[44]
Arenicolide A	*Salinispora arenicola*	[46]
Marinomycins	*Marinispora* sp.	[47]
Bonactin	*Streptomyces* sp.	[48]
Rifamycin	*S. arenicola*	[49]

Cancer stands as a paramount health concern necessitating significant attention. Numerous compounds sourced from marine actinomycetes serve crucial roles as anti-cancer agents. These antitumor compounds operate through mechanisms such as apoptosis induction via DNA cleavage facilitated by topoisomerase I or II inhibition, mitochondrial permeabilization, suppression of pivotal enzymes involved in signal transduction like proteases, modulation of cellular metabolism, and in certain instances, inhibition of tumor-induced angiogenesis [50]. Table 5 shows some anti-cancer compounds isolated from marine actinomycetes.

Table 3: Anti-cancer compounds isolated from actinomycetes

Anticancer Compounds	Source	Reference
Pyridinium	*Amycolatopsis alba*	[51]
Macrolactam	*Streptomyces* sp.	[52]
Usabamycins	*Streptomyces* sp.	[53]
Neomarinones	*Actinomycetes* sp.	[54]
Piericidins	*Streptomyces* sp.	[55]

The foremost study of the structural activity relationship of potent antibiotic merochlorin A has been carried out, with 16 analogs produced using biosynthetic lead compounds, numerous Gram-positive, drug-resistant bacteria and low toxicity profile to human cell lines were also identified. The biodata for this derivative was disproportionate to that of the NP and highlights the potential of merochlorin chemo type as a new class of antibiotics [56].

7.Bioactive Secondary Metabolite from Marine Fungi

The marine fungi predominantly those isolated from marine sediments, alga, sponges and invertebrates, seem to offer a wealth of secondary metabolites with properties such as antibiotic, antifungal, and anticancer effects. Recent studies exploring these organisms for bioactive secondary metabolites highlight their significant potential as a reservoir for novel therapeutic compounds [57]. The Aspergillus and Penicillium genera of fungi are major organisms, which produced superseding of the reported marine fungal compounds [58]. While musters of genus Penicillium is among the most studied fungi and represents an imperious drug producer, such as Penicillium griseofulvum (griseofulvin producer), *Penicillium chrysogenum* (penicillin producer) and, many heretofore undefined natural products continue to be found within Penicillium fungi [59,60]. As of today, plinabulin stands as the sole synthetic analog derived from marine fungi to have progressed into clinical phases. Plinabulin is a unique vascular-disrupting agent that shows strong interruption of tumor blood flow because of the interruption of tumor vascular endothelial cells, causing tumor necrosis [61].Table 6 shows some marine fungi that produced peptides with biopharmaceutical potential [62].

Table 4: Marine peptides that derived from fungi have biopharmaceutical potential

Source	Activity	Inhibition
Aspergillus terreus	Antiviral	Anti-HIN1
Leucostoma persoonii	Antibacterial	*Staphylococcus aureus*
Trichoderma sp.	Antituberculosis	Mycobacterium tuberculosis
Aspergillus fumigatus	Antiprotozoal	*Trypanosoma brucei*

Moreover, new sampling techniques and development of deep-sea instrumentation have established a novel and highly significant source for marine fungal biodiversity [63]. Purpuride D isolated from Penicillium chrysogenum showed antimicrobial bioactivities against *C. albicans, E. coli* and MRSA with MIC values ranging from 3 to 8 μg/mL [64]. By applying advanced approaches and strategies in the

exploration of secondary metabolites from cultured marine fungi, we anticipate uncovering a diverse array of unique bioactive natural products. Among these, there may be excellent candidates for drug development, presenting a potential treasure trove of therapeutic agents. Marine fungal strains exhibit high potential for generating a diverse array of secondary metabolites, including polyketide-derived alkaloids, terpenes, peptides, and compounds synthesized through mixed biosynthesis pathways [64, 65].

8.Contemporary techniques for screening Marine drugs

Modern drug screening heavily relies on high-quality compound libraries such as Streptome databases. Yet, compared to synthetically prepared compounds, natural products (NPs), especially those sourced from marine environments, pose challenges in isolation and are seldom available in vendor catalogs. Nevertheless, these compounds are considered valuable additions to screening libraries, facilitating marine natural product drug discovery [66, 67]. Because of their complex stereochemistry, natural products are frequently more selective than synthetic compounds, making them particularly well-suited for targeting challenging, low-druggable targets [68]. Figure 4 illustrates the distribution of various marine species and the isolation of compounds from either marine organisms or microbes associated with the marine environment.

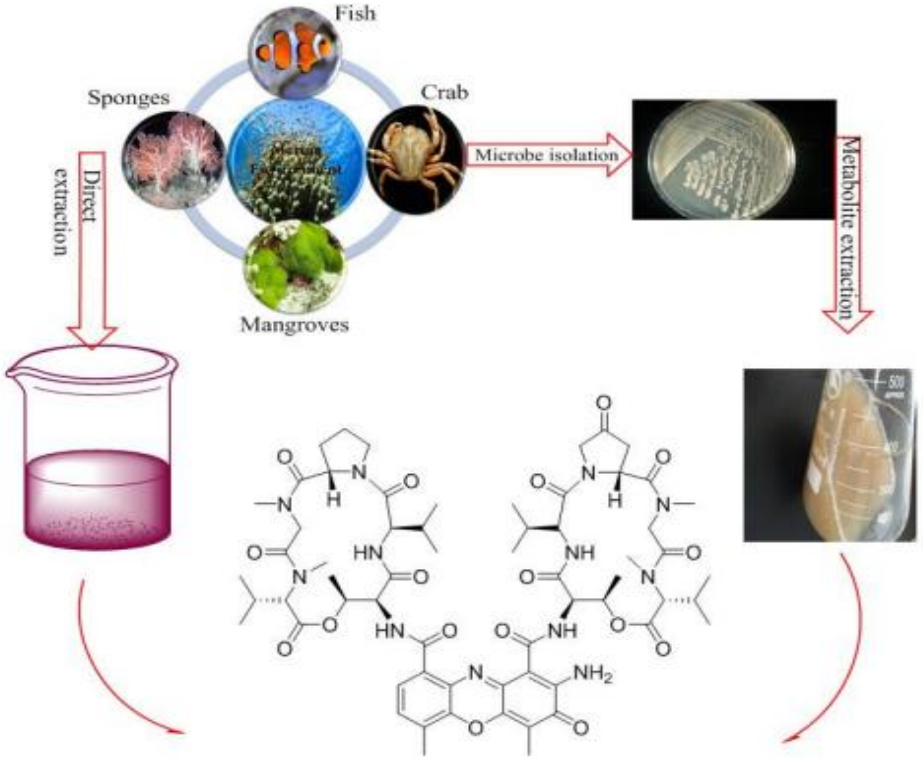

Figure 4: Studying the distribution of diverse marine life forms and isolating compounds from marine resources

Exploration of marine pharmaceuticals has traditionally prioritized conspicuous organisms like sponges, corals, tunicates, and macroalgae. However, there's been a growing focus on marine microbes in

recent years, leading to significant discoveries of bioactive compounds like salinosporamide A [69]. A novel approach to uncovering typically hidden bacterial metabolites involves retrieving expressed and secreted natural products (NPs) in their natural environment, made feasible by advancements in analytical and informatic technologies. Environmental stimuli are thought to trigger the expression of Natural Products that remain dormant under conventional laboratory conditions. [70]. Hence, the capturing and analysis of metabolites produced in their natural environment complement conventional culture-based methods, providing novel perspectives into the roles of marine microbial natural products. This innovative method has enabled the discovery of numerous known marine bacterial metabolites, such as staurosporine [71]. The investigation of marine organisms for valuable macromolecules has been largely overlooked due to the intricate techniques required. This includes the search for beneficial proteins from marine sources, such as the antiviral cyanobacterial proteins like cyanovirin and scytovirin, as well as glycoproteins like the antiviral lectin griffithsin found in red algae, which has shown promise against viruses such as SARS-CoV-2 [72].

9.Novel Methodologies in the Investigation of Marine Natural Products

Drug research and development is inclusive, time-consuming, expensive, and complex process. A 2016 research described a rate of clinical success. The probability that a drug enters into clinical probationary is of 12%. At this time, the development of a pharmaceutical agent from concept to its commercial release needs 12–15 years and requires 2–3 billion US dollars [72]. Various new approaches to reduce the testing process and costs have been developed and implemented in drug research and development. At sundry stages of drug development, computational workflow has proved to be contributory and endure to be requisite in the ongoing demand for life-saving drugs. Throughout the past several years, Computer-aided drug design (CADD) techniques have emerged as powerful tools in drug development. Predicting the biological activities of natural products (NPs) using computers is essential for guiding decisions regarding in vivo and in vitro testing of isolated NPs and extracts. It also aids in designing bioactive derivatives of NPs and virtually screening databases of known NPs. Furthermore, chemical space regions encompassing NPs are acknowledged as promising areas for discovering new drug leads, as they represent chemical structures optimized over millions of years for efficient performance in biochemical processes. [73]. Skariyachan et al. [74] utilized computational techniques to identify lead compounds targeting the Ebola virus, sourced from marine sponges. Figure 5 describes the computational workflow that leads to marine natural product discovery.

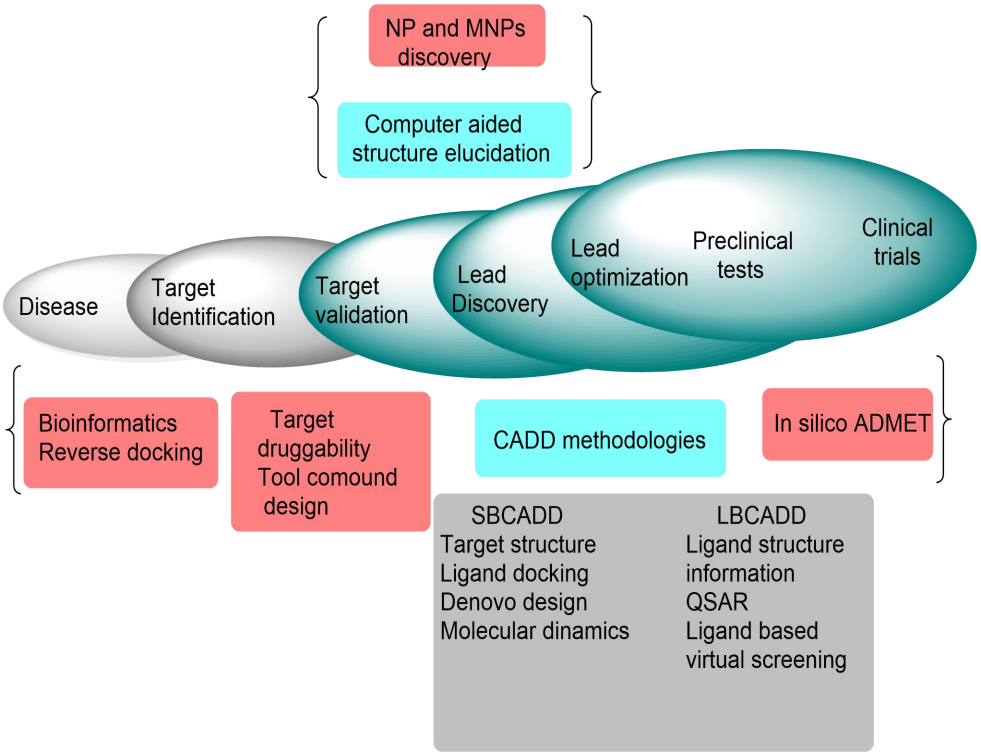

Figure 5: Computational workflow that leads to marine natural product discovery

Various analytical methods, including liquid chromatography-mass spectrometry [75, 76], liquid chromatography time-of-flight MS [77], high-resolution electrospray ionization mass spectrometry, and NMR spectroscopy, have been employed for comprehensive data analysis. This approach aims to minimize redundancy in isolation procedures, thus optimizing efficiency [76]. Roullier *et al.* [78] reported the new bioactive metabolites and their halogenated metabolome from marine derived fungi. An innovative software program, MeHaloCoA, was established to systematize the characterization of halogenated compounds in HPLC-MS profiles and revealed by the isolation and recognition of two novel MNPs of chlorogriseofulvine and griseophenone I with antiproliferative activity from fungus *Penicillium canescens*. Since 2014, substantial progress has been made in unraveling the intricacies of biosynthetic pathways, leading to a better grasp of regulatory mechanisms, heterologous expression, and manipulation of large DNA sequences. These advancements, along with heightened participation from North Asian countries over the past decade, have greatly contributed to marine drug discovery and biotechnology. The increased emphasis on marine microorganisms has further bolstered these efforts. Despite these strides, there remains a vast realm of marine life waiting to be explored, promising ongoing innovation and the development of tangible products to enhance human health. This momentum supports the cultivation of a robust and sustainable 'blue economy.'

10.Conclusion

Marine natural products (NPs) offer significant potential for inspiring drug discovery, with higher prospects of yielding clinically valuable drugs compared to other sources. Advances in sampling methodologies, such as the targeting of microbial mutualists and the slow-growing bacteria in nutrient-depleted regions, coupled with the exploration of novel habitats such as the deep sea, have headed to the identification of previously unexplored natural products. Enhanced dereplication strategies are sharpening

the focus on uncovering new marine NPs. Altogether, these novel methods and collaborative approaches are significantly boosting the success rate of drug discovery endeavors from marine sources.

11.Limitations and Further Studies

Despite the promising advancements in marine natural product (NP) research, there are still some limitations and areas for future studies that warrant consideration. Firstly, while sampling techniques have improved, accessing certain marine environments, such as extreme depths or remote locations, can still be challenging and costly. Future research could focus on developing more efficient and cost-effective methods for sampling these environments. Secondly, although exploration of new habitats has led to the discovery of novel NPs, there are still vast areas of the ocean that remain unexplored.

Further exploration of these regions could uncover even more diverse classes of NPs with potential therapeutic benefits. Future studies could focus on fostering more interdisciplinary collaborations between marine biologists, chemists, pharmacologists, and clinicians to fully leverage the potential of marine NPs in drug discovery.

Overall, while the future of marine NP research is promising, addressing these limitations and pursuing further studies will be essential for maximizing the potential of marine NPs in addressing challenging medical conditions and improving human health.

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