TMR Trends in Medical Research

OPEN ACCESS

Pivot Role of Bioinformatics in Drug Discovery Using Marine Natural Products as Resources

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ABSTRACT

Many attainments have occurred in the 20th Century, especially in modern pharmaceuticals. New drug therapies have extended human life span and improved the quality of life. In this regard, society has become more and more reliant upon the availability of safe and efficacious pharmaceutical products. Nature plays the main source of providing medicines that offer the source of new pharmaceuticals. Today, over 50% of marketed drugs are either extracted from natural sources or produced by synthesis using natural products as templates. Since ancient times, man used natural medicines generally as crude extracts from plants to treat infection, inflammation, pain and a variety of other maladies. Studies and Investigations held in these "natural" ethnobotanical preparations led to the isolation of compounds whose beneficial properties have provided the foundation of the current pharmaceutical industry. New diseases due to changing environment and many diseases without effective drugs decide on the drug manufacturers for new resources to develop effective and safe drugs for the increasing demands of the world population. Recently, the major focus is upon the marine environment for the reason that marine organisms possess bioactive substances required for the human race and also the ocean is a less explored source of environment. The processes of designing a drug using bioinformatics tools open a new area of research. Virtual screening of the target disease for compounds that bind and inhibit the protein aids in bioinformatics steps. This review offered the marine environment as an ensuring source for drug discovery, some successful drugs in use from marine products, several databases in use and the application of bioinformatics to deliver a successful drug.

KEYWORDS

Drug target, marine bioactive substances, proteomic data, structural biology and transcriptomics, metabolomics, phenotypic screening, ribosome profiling

INTRODUCTION

There is a continual need for new therapeutic agents, especially to treat a large variety of diseases for which there are no effective therapies. Many forms of cancer, viral and fungal infections, inflammatory diseases and neurodegenerative diseases cannot be treated successfully. Development of resistance of pathogenic microorganisms to antibiotics and cancer cells to antitumor drugs requires the compensatory generation of new drugs. Some microorganisms such as bacteria, fungi and aquatic creatures synthesize bioactive secondary metabolites known as natural products. The discovery of natural products from

ISSN: 2151-6065 (Online)
ISSN: 1819-3587 (Print)
https://doi.org/10.3923/tmr.2023.58.68

Received: 24 Feb. 2023
Accepted: 14 Jul. 2023
Published: 4 Aug. 2023

different organisms in nature can be a great contribution to the field of drugs in the future. The biological diversity of the ocean offers a vast area for the discovery of these secondary metabolites since representatives of every phylum are found in the sea. The ocean contains more than 200,000 described species of invertebrates and algae, however, it is estimated that this number is a small percentage of the total number of species that have yet to be discovered and described. Modern Bioinformatics and the increasing availability of sequenced genomes offer more opportunities than ever for the discovery of novel bioactive compounds and biocatalysts from marine organisms. The identification of biosynthetic genes and gene clusters through the bioinformatics approach and their eventual heterologous expression will give a great impulse for natural product identification and drug discovery from marine organisms. This review presents a comprehensive overview of Drug discovery from marine natural products, some success stories of it and the role of bioinformatics in making the challenge easy[1].

Life on the earth has its origin in the ocean and is believed to be evolved from common ancestors. Since two-thirds of the world's marine species are still unidentified, it's necessary to step out to explore marine biodiversities, because the ocean represents a virtually untapped resource for the discovery of novel chemicals with pharmaceutical potential. Marine plants, animals and microbes produce compounds that have potential as pharmaceuticals. Chemicals that are not needed by the organism for their basic or primary metabolic processes are called "Secondary Metabolites" and they are believed to confer some evolutionary advantage. Most of these plants and animals have evolved chemical compounds to help defend against predators to attract or inhibit other organisms from settling or growing on them and to provide chemical cues to synchronize reproduction among organisms that expel their eggs and sperm into the water[2]. What man can benefit from these is the mechanisms by which these organisms prevent encroachment or predation interact with the same or similar enzymes and receptors that are involved in human disease processes. For example, many natural products have been identified that inhibit cell division, the process that is the primary target of many anticancer drugs. In most cases, there is a greater understanding of the effect of the natural product on human disease processes than of the function in the marine organism from which it was isolated. The marine environment became a focus of natural products drug discovery research because of its relatively unexplored biodiversity compared to terrestrial environments.

It was Bergmann who introduced the potential of marine natural products as pharmaceuticals in the 1950s[3,4]. There are two marine-derived pharmaceuticals that are clinically available today. The anticancer drug, Ara-C, is used to treat acute myelocytic leukemia and non-Hodgkin's lymphoma. The antiviral drug, Ara-A, is used for the treatment of herpes infections[5]. Both are derived from nucleosides isolated from shallow water marine sponge belonging to the Coast of Florida. Marine sponges are among the most prolific sources of diverse chemical compounds with therapeutic potential. Of the more than 5000 chemical compounds derived from marine organisms, more than 30% have been isolated from sponges. Other marine sources of bioactive molecules with therapeutic potential are bryozoans, ascidians, molluscs, cnidarians and algae. Several strains of phytoplankton, especially cultured species of diatoms, have been described as exhibiting antibacterial and antifungal activity[6]. However, the levels of activity are low and hence the active compounds have not yet been isolated or characterized. of several steps are involved in designing a drug such as identification of the target disease, studying the interesting compounds, detection of the molecular bases for disease, rational drug designing techniques, refinement of compounds, Quantitative Structure-Activity Relationship (QSAR), the solubility of the molecule and drug testing. The key characteristics of drugs are Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) and efficacy. Although these properties are usually measured in the lab, they can also be predicted in advance with bioinformatics software to save cost. So the present review was framed to emphasize the comprehensive overview of drug discovery from marine natural products with the support of some success stories and making the challenge easy through the role of Bioinformatics.

SUCCESSFUL DRUGS FROM MARINE ENVIRONMENT

There are seven therapeutic agents derived from the marine environment. Of these four are anticancer, one antiviral, one pain control and one for hypertriglyceridemia[7]. In addition, a further 13 agents are in phase I, II or III clinical trials. Most of the collected sources of organisms yielded these agents reveal mollusks, tunicates and sponges as the richest sources of these valuable substances. But it's shown that these organisms often feeding upon the microorganisms that are the actual producers of the bioactive agents. Microorganisms are regarded as the real metabolic jewel of Worlds Ocean, especially the heterotrophic bacteria and cyanobacteria. About 80% of them are in clinical trials and approved pharmaceutical agents.

Cytosine arabinoside: An early marine drug discovery occurred from a Caribbean sponge *Cryptotethia crypta,* which possessed metabolites with a very interesting but relatively simple modification of a nucleoside, the normal 2-deoxyribose ring of deoxythymine and uracil are replaced by β-D-arabinofuranose[8]. It was revealed that cytosine arabinoside was a potent disrupter of DNA replication and led to cellular toxicity[9], while the arabinoside derivative of adenosine had antiviral effects[10]. Metabolic activation of Ara-C to the corresponding triphosphate yields a substrate mimic of deoxycytidine 5'-triphosphate and following incorporation into the DNA backbone, inhibits the DNA polymerase as well as DNA repair enzymes. While Ara-C has found the greatest utility in inducing remissions of acute myelocytic leukemia, more significantly these discoveries from nature helped illuminate nucleoside chemistry as a viable therapeutic strategy that later gained favor in antiviral chemotherapy.

Ecteinascidin 743 (ET-743): ET-743 also known as Trabectedin is a second discovery of unusual nucleoside sponge-based chemistry, potent anticancer activity was detected in extracts of the tunicate *Ecteinascidia turbinata*. It is sold under the brand name Yondelis and used as an antitumor chemotherapy medication for the treatment of advanced soft tissue sarcoma and ovarian cancer. It's nearly 30 years until the structure of the active compound, ecteinascidin 743 (ET-743 = trabectedin), was finally elucidated[11,12]. Ultimately, this need was met by semi-synthesis from the microbial natural product, Cyanosafracin B, a fermentation product of the bacterium *Pseudomonas fluorescens*[13]. On cells, the mechanism of action of ET-743 interacts with DNA and results in a G2/M block and ensuing p53-independent apoptosis. The subcellular target has been identified as the minor groove of DNA; once bound, it interferes with the functioning of the nucleotide excision repair system to bring about a cytotoxic effect[14].

Halichondrin B: It is the third marine anticancer agent drug discovered in 1986 from the sponge *Halichondria okadai* by Jordan *et al*.[15]. The natural product was subsequently shown to possess exquisite cancer cell toxicity through an antitubulin mechanism, perhaps having a new mechanism of action by binding near the vinca site on β-tubulin but having rather different biochemical effects, including microtubule dynamics, as compared with other agents[16]. It was later found that the macrocyclic portion of the molecule was responsible for the potent biological activity and this could be enhanced through modification of the macrolactone functionality to a macrocarbocyclic ketone, giving rise to eribulin[17]. Eisai Pharmaceuticals in the US recently launched this agent under the product name Halaven and it is quickly finding utility in the treatment of drug-refractory breast cancer[18].

Dolastatin 10: The most recent discovery approved anticancer agents from the marine environment is brentuximab vedotin, a chimeric antibody attached through a protease cleavable linker to a derivative of the potent antitubulin agent dolastatin 10[19]. Dolastatin 10 was first reported in 1987 by the Pettit group. It was actually isolated from the Indian Ocean Sea hare *Dolabella auricularia*[20] and was later found to originate from the gastropod's cyanobacterial (*Symploca* sp.) diet[21]. Phase I and II clinical trials of dolastatin 10 and the water-soluble analog auristatin P2E were unsuccessful due to a lack of efficacy and induced peripheral neuropathy. However, linking another analog of dolastatin 10, namely monomethyl

auristatin E, to an antibody that targets CD30, a cell membrane protein present on the surface of Hodgkin's lymphoma cells resulted in a highly effective and well-tolerated agent, brentuximab vendotin[22]. An accelerated FDA approval of this agent for use in Hodgkin's lymphoma and anaplastic large cell lymphoma was granted in August, 2011 and is marketed as Adcetris® by Seattle Genetics.

Ziconotide: It is also known as intrathecal ziconotide because of its administration route. It is a peptide toxin from the fish-hunting marine mollusk, Conus magus, a cone snail. It has found utility as a therapeutic for severe and chronic pain[23]. The ω-conotoxin peptide known as ziconotide (Prialt) functions through binding as an antagonist to N-type voltage-gated calcium channels. Because of its peptide nature, it must be administered as an infusion directly into the cerebrospinal fluid much like it is injected via a harpoon-like structure in nature to immobilize its prey. For patients with severe chronic pain, this is a useful agent and has the additional benefit of not inducing tolerance. Additional conotoxins are in clinical development with potential applications in pain management and are widely employed tool compounds in neurotoxin research[24].

Marine origin of 13 agents with a few in current clinical trials, 11 with an indication for cancer, one for cognition and schizophrenia, one for Alzheimer's (along with cancer) and one for wound healing. Interestingly, one of 3 of these agents are in phase II trials and two in phase I trials. They are antibody conjugates of dolastatin 10 analogs and are closely related to brentuximab vedotin. Thus, it is promising that marine-derived agents are very strong and will certainly see several of these agents enter the marketplace and clinic in the coming years[11]. Kainic acid from the red alga, saxitoxin from Alaskan butter clams and tetrodotoxin from the Puffer fish are some of the early discoveries along these lines and the latter two agents were critical in defining sodium channel function. Subsequently, several commercial providers offer marine natural products for sale as research biochemicals.

BIOINFORMATIC SOFTWARE AND DATABASES

Modern drug design for potential new medicines relies on the ability to predict the effectiveness of small molecules that bind to a biological target. To meet the need for faster and more accurate measuring of drug shapes and to achieve the best binding bioinformatic tools are required. An extensive compilation of software, databases and web services directly related to drug discovery can be found at http://click2drug.org/ maintained by the Swiss Institute of Bioinformatics. These are roughly grouped into (1) Databases, (2) 1720 Current Topics in Medicinal Chemistry, 2017, Vol. 17, No. 15 Xuhua Xia chemical structure representations, (3) Molecular modelling and simulation, (4) Homology modeling to infer the structure of a protein guided by a homologue of known structure, (5) Binding site prediction, (6) Docking, (7) Screening for drug candidates, (8) Drug target prediction, (9) Ligand design, (10) Binding free energy estimation, (11) QSAR and (12) ADME Toxicity.

Many of the software packages supported by well known institutions are powerful and free. These include databases such as ChEMBL and SwissSidechain, software tools such as UCSF Chimera which is not only a 3D visualization tool but also a platform for software developers interested in structural biology, SwissSimilarity for virtual screening, SwissBioisostere for ligand design, SwissTargetPrediction, SwissSideChain to facilitate experiments that expand the protein repertoire by introducing non-natural amino acids and SwissDock for docking drug candidates (small molecules) on proteins. They typically have free versions for students and teachers, although some software are commercial, e.g., CHARMM and PyMOL (Schrödinger).

OMICS RESOURCES FOR DRUG DISCOVERY

Genomics: An interdisciplinary field of biology focusing on the structure, function, evolution mapping and editing of genomes. A genome is a complete set of DNA in an organism including all of its genes as well as a hierarchical, three-dimensional configuration.

Transcriptomics: Techniques used to study an organism's transcriptome, the sum of all its RNA transcripts. The information content of an organism is recorded in the DNA of its genome and expressed through transcription. Transcriptomic technologies provide a broad account of which cellular processes are active and dormant. A major challenge in molecular biology lies in understanding how the same genome can give rise to different cell types and how gene expression is regulated.

Proteomics: Proteins are responsible for an endless number of tasks within the cell. The complete set of proteins in a cell can be referred to as its proteome and the study of protein structure and function and what every protein in the cell is doing is known as proteomics. The proteome is highly dynamic and it changes from time to time in response to different environmental stimuli. The goal of proteomics is to understand how the structure and function of proteins allow them to do what they do, what they interact with and how they contribute to life processes. An application of proteomics is known as "protein expression profiling" where proteins are identified at a certain time in an organism as a result of the expression to a stimulus. It can be used to develop a protein-network map where interaction among proteins can be determined for a particular living system. It can also be applied to map protein modification to determine the difference between a wild type and a genetically modified organism.

Metabolomics: It is one of the newest 'omics' sciences. The metabolome refers to the complete set of low molecular weight compounds in a sample. These compounds are the substrates and by-products of enzymatic reactions and have a direct effect on the phenotype of the cell. Metabolomics aims at determining a sample's profile of these compounds at a specified time under specific environmental conditions. It can be used to determine the difference between the levels of thousands of molecules in a healthy and diseased organism.

TRANSCRIPTOMICS AND DRUG DISCOVERY

Transcriptomic data have been widely used to determine the transcriptional structure of genes, in terms of their start sites, 5′ and 3′ ends, to identify differentially regulated genes, alternatively spliced isoforms and different transcription start and termination sites between patient and matched control. Transcriptomic data analysis contributes to drug discovery mainly in two ways, one in phenotypic screening to identify and refine drug candidates and the other in drug target identification.

PHENOTYPIC SCREENING

Substance such as small molecules, peptides or RNAs can alter the phenotype of a cell or an organism. The screening process that helps to identify such substances is called phenotypic screening. Bioinformatics can contribute to gene expression and drug discovery by formulating an objective and rational index of drug desirability (I_{dd}) in phenotypic screening studies with gene expression profiles as phenotypes. Such an I_{dd} would complement therapeutic indices[25] based on various pharmacokinetic models for evaluating drug effects and safety under various drug concentrations. The lack of an explicit I_{dd} may have contributed to the low rate of successful drugs discovered through phenotypic screening.

DRUG TARGET IDENTIFICATION

The disease occurs as a result of abnormal changes in gene expression or regulation. But interpreting the cause and effects of the disease becomes more difficult as a gene shows its disease-causing expressions in time t1 and causes the expression of many other genes at time t2. Unfortunately, t2 may occur years after t1. So it may cause false interpretations of gene expression patterns between the control and disease groups.

Transcriptomic data analysis has revealed that most of the human genome is transcribed. Because RNA interference can modulate many cellular processes and RNA has been recognized as a new type of drug,

mining transcriptomic data may uncover many RNA molecules either as drugs or as drug targets. From an evolutionary point of view, a functionally important sequence is expected to be conserved among related species, such as within apes or primates. One can identify functionally important RNAs among millions of different transcripts by checking sequence conservation with one of the numerous bioinformatics tools. Any functionally important RNA species may be a potential drug target[26-28].

PROTEOMIC DATA AND DRUG DISCOVERY

Proteomics has such significance in the field of drug discovery due to the central role proteins play in establishing the biological phenotype of organisms in a healthy and diseased state. They are the workhorses in living cells. A transcribed gene may be differentially translated[29,30] or not translated[31] and different proteins have different degradation rates, so transcriptomic data is often not a good predictor of protein abundance. For this reason, characterizing and comparing proteomes between patient and control is often more effective in identifying drug targets than genomic or transcriptomic data. Proteomic data have been obtained from nearly all model organisms and deposited in public databases such as PaxDB[32]. Such data have greatly facilitated the development[33] and application of indices predicting translation efficiency[34-36]. Bioinformatics tools used for proteomic data analysis are similar to those in transcriptomic data, i.e., using proteomic data for phenotypic screening and drug target discovery. Most proteomic data are used in comparisons either between treatment and control animals[37-39] or between patients and matched normal control[40]. For example, caffeine-treated rats differ in protein expression from control rats[41]. Numerous such relationships between drugs and protein targets have been reported and stored in databases[42-44] to facilitate retrieval of possible interactions of a query drug with proteins. Proteomic data, without following a cohort over time, suffer from the same problem as genomic and transcriptomic data in the causal interpretation. In particular, it is difficult to identify which disease is caused by differential expression observed in many proteins. Different proteins change their abundance at different cell cycle phases. Without considering temporal and spatial heterogeneity of cells taking, comparison of protein profiles (or transcriptomic profiles) between matched patient/normal pairs will continue to pump out false positives that have little relevance to drug discovery. In animal models, it is possible to sample cells over different periods. This made the single-cell characterization of transcriptomes and proteomes[45-47] overtime to reconstruct a cell cycle profile of gene expression.

RIBOSOME PROFILING AND DRUG DISCOVERY

Protein abundance data have limitations because (1) Low-concentration proteins, short peptides, or transient proteins often cannot be detected and (2) Membrane proteins, which often serve as essential components in signal transduction, are difficult to isolate, separate and purify. Transcriptomic data once spawned the hope that proteomic data can be predicted from transcriptomic data, but differential translation efficiencies among mRNA[48] and degradation efficiencies among proteins distort the relationship between mRNA abundance and protein abundance. However, ribosome profiling data, coupled with transcriptomic data, are expected to generate good predictions of protein production rate. Transcriptomic and ribosome profiling data provide information on mRNA abundance and translation efficiency, respectively. If genes A and B have mRNA abundance values NA and NB, respectively, from transcriptomic data and their translation efficiency is RA and RB, respectively, from ribosome profiling data, then their relative protein production rate is NA*RA and NB*RB, respectively. Differences between such predicted protein abundance and observed protein abundance can be used to measure protein degradation rate. Such prediction should be facilitated by obtaining transcriptomic and proteomic data in the same experiment[49], ideally from a single cell[50-52].

STRUCTURAL BIOLOGY AND DRUG DISCOVERY

An ideal bioinformatics platform for drug discovery based on structural biology helps one to (1) Predict 3-D structure of a protein or RNA based on the cellular environment where it is translated or

transcribed, (2) "BLAST" a known protein/RNA structure against databases of protein/RNA structures to retrieve all protein/RNA with similar structures to facilitate structure-function interpretations and assessment of functional redundancy of the query protein in the cell and to understand structural convergence, e.g., non homologous proteins or RNAs with similar structures[53,54], (3) Identify and retrieve all potential binding partners of a given query structure to facilitate the assessment of the query's potential as a drug target or drug candidate, i.e., its efficiency and side effects as a consequence of physical interactions with other cellular components, (4) Automatically identify proteins and RNA that can form a complex and assemble such complexes (e.g., ribosome and spliceosome) through structural modeling and simulation, (5) Predict the function of protein/RNA with known structure, either alone or as a component in a complex and (6) Suggest new structures that can physically interact with the query to activate/deactivate the query protein/RNA function in the cell. Almost all of these can be done, although not perfectly, by databases and software tools compiled at http://www.click2drug.org/.

When one has a protein of interest, the first is to check if its structure already exists in PDB[55,56]. If not, then one can use tools such as homology modelling to infer its structure based on one or more close homologues with known structures. Such tools include SWISS-MODEL[57] and TASSER[58] and their derivatives. Once the structure is refined, one can use UCSF Chimera[59] or PyMOL (The PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC) to visualize the structure and use automated screening software such as SwissSimilarity[60] to identify potential drug candidates that can interact with the protein of interest. Such a screening approach is greatly enhanced by metabolic and ligand databases such as ChEMBL[61] and SuperSite[62]. Such analyses not only shed light on identifying drug-target interactions, but also facilitate the identification of side effects of individual drugs, e.g., a drug that can bind to many biologically important enzymes in humans is almost sure to have many side effects, but a drug that does the same in a pathogen would be quite desirable.

One may also use docking software such as SwissDock[63] to study physical interactions between protein and small molecules or use SwissBioisostere to design and refine ligands. In one well-documented protein-ligand interaction, it is natural to infer that other proteins with similar sequences or structures may also bind to the ligand. Such a similarity-based approach is the conceptual foundation for the software SwissTargetPrediction. It is important to keep in mind that a structure determined by X-ray crystallography or by NMR represents only a snapshot of structural dynamics and that protein structure can change in response to different cellular environments. The software CHARMM and its derivatives facilitate the characterization of such dynamic interactions of proteins with their binding partners. Such studies are facilitated by general databases of drug-target interactions and special databases documenting protein interactions in cancer cells or organism-specific databases such as that for *Mycobacterium tuberculosis* or in membranes involving GPCR-ligand associations.

CONCLUSION

Most of the marine organisms' genome is not mapped and researchers are trying their best in this field to produce new effective drugs. Numerous new marine species are discovered every year. Like terrestrial species, marine organisms (both microorganisms and macroorganisms) produce secondary metabolites. These secondary metabolites are useful to mankind because they can be used to produce drugs. Some drugs are available in the market and some are in trial. Nowadays there is much urgency in the discovery of new drugs as many diseases are newly appearing. Some diseases do not have efficient drugs due to many disease pathogens acquiring resistance against the drugs in use. The advance in Bioinformatics genome mapping as well as drug designing became easier. This study will help the researchers about the need for ocean exploration, the importance of marine organisms and bioinformatics in the field of drug discovery, some marine-derived drugs in use and the challenges in the drug discovery sector.

SIGNIFICANCE STATEMENT

Marine biodiversity is a vast area to obtain the secondary metabolites from organisms. Bioinformatics in drug designing and discovery for the production of effective drugs. Cytosine arabinoside, Ecteinascidin 743, Halichondrin B, Dolastatin 10, Ziconotide, etc are some of the successful marine origin drugs in the market and some drugs are in trial. This study defines how structural biology helps in drug discovery, i.e., it helps to predict the 3-D structure of a protein/RNA, to retrieve all protein/RNA with similar structures to facilitate structure-function interpretation, identification and retrieve all potential binding partners by which the efficiency and side effects of the drugs can be detected and major databases and software tools are also cited.

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