International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319-6718, ISSN (Print): 2319- 670X
www.ijpsi.org Volume 13 Issue 3 ǁ May. –June, 2024 ǁ PP. 48-50

A Review on Marine Drug Discovery Through Computer Aided Drug Design

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Abstract:
Marine organisms represent a vast and largely untapped resource for drug discovery. Computer-Aided Drug Design (CADD) has emerged as a powerful tool in the exploration of marine bioactive compounds for pharmaceutical applications. This review provides an overview of recent advancements in marine drug discovery facilitated by CADD techniques. It discusses the various computational methods employed, such as molecular docking, virtual screening, and pharmacophore modeling, in the identification and optimization of lead compounds from marine sources. Furthermore, it highlights the challenges and future prospects in the field, including the integration of omics data and artificial intelligence approaches for more efficient drug discovery pipelines.

Keywords:
Marine drug discovery, Computer-Aided Drug Design (CADD), molecular docking, virtual screening, pharmacophore modeling, omics data, artificial intelligence, lead compounds.

I. Introduction:

The Special Issue "Marine Drug Discovery through Computer-Aided Approaches" was created with the objective of mapping the current scientific actors in the field of computer-aided approaches applied to blue biotechnology, and of providing a comprehensive overview of the great variety of advanced computer-aided methods for the discovery and identification of molecular agents with added value and health-promoting properties for the development of medical and biotechnological applications.[1]

This Special Issue invited the blue biotechnology community working with computer-aided technology to submit original research, reviews, and perspectives in all steps of the marine biotechnology development pipeline including computer-aided methods; from blue biotechnology, drug discovery, drug repurposing, chemo informatics, bioinformatics, dereplication , MNPs databases, machine learning techniques, biological and chemical space, Quantitative Structure–Activity Relationship (QSAR), molecular docking, Computer-Aided Drug Design (CADD), and Computer-Assisted Structure Elucidation (CASE), generating a compilation of processes and technologies.[2]

The aim was also to develop a "guidebook" for maximizing the impact of marine biotechnology development that can be used to start, improve, and facilitate collaborations between related and complementary scientific fields, by providing information, expert contacts, and their expertise that will, both directly and indirectly, improve the discovery and innovation in blue biotechnology and boosting blue bioeconomy using computing methodologies. Computer-aided drug design (CADD) techniques allow the identification of compounds capable of modulating protein functions in pathogenesis-related pathways, which is a promising line on drug discovery.[3]

Marine natural products (MNPs) are considered a rich source of bioactive compounds, as the oceans are home to much of the planet's biodiversity. Biodiversity is directly related to chemodiversity, which can inspire new drug discoveries. Therefore, natural products (NPs) in general, and MNPs in particular, have been used for decades as a source of inspiration for the design of new drugs. However, NPs present both opportunities and challenges.[4]

Marine Drug Discovery :

The use of nature to obtain medication has often piqued people's interest. Natural products are thought to have the advantages of possessing a wide range of structural and chemical diversity, improved protein binding properties (due to their complex structure), and specific biological activity. There are also strong lead compounds that can be modified further.[5] Oceans occupy 70% of the planet's atmosphere. More than 300,000 species of invertebrates and algae can be found in the oceans.[5] Coral reefs, the world's largest living structures, are among the world's greatest biodiversity storehouses.

These ocean rainforests cover 284,300 square kilometres and are home to around 2 million plants and animals, as well as a quarter of all marine fish.[6] Today's exciting pharmaceutical research is increasingly focused on the sea, where marine organisms have developed secondary metabolites to target prey or protect their environment . Antitumor, antiinfective, antiangiogenetic, and nutritional properties are all present in these metabolites.[7] As a result, we must take advantage of the therapeutic value of these extracts.

For different therapeutic indications, a wide range of marine drugs has been licenced. Prialt (Ziconotide), a pain reliever derived from the venom of the cone snail Conus magus, is used to treat cancer, AIDS, and other neuropathies . Lovaza (Ethyl esters of omega-3 fatty acids) is a therapy for hypertriglyceridemia made from fish oils. [8] A large number of drugs and extracts with promising potential are currently undergoing clinical trials and studies.

Aplidine is being used in a phase III trial to treat multiple myeloma.[9] Drug procurement, on the other hand, is a difficult process that necessitates both technology and expertise. It is critical to obtain pure extracts in adequate amounts when researching a potential drug. Adequate funding is also a necessary condition for study. Any of the medications could be withdrawn from clinical trials due to insufficient effectiveness or toxicity. This could result in significant financial losses.[8] As a result, researchers must overcome obstacles at every stage of the research process, from extract sampling to drug approval.

A brief discussion of a few promising marine drugs is presented in this study. It also includes a list of medications that are currently being researched for their therapeutic potential.

II. Material And Method:

Initial dataset of 10 compounds was generated from the database owned by Professor Avila. This library is composed of the molecules she has studied and collected over the years. The selection of the initial 10 compounds was done manually, based on their chemical diversity and easy accessibility, to include both chemodiversity and biodiversity representatives.[10]

Cabrakan, two-dimensional (2D), and Hurakan, three dimensional (3D), ligand-based virtual profilings (VP) tools were employed as in . VP experiments were carried out using marine molecules described in as a seed. Cabrakan uses the Tanimoto coefficient to compare molecules, through the use of 2D (Morgan/circular) fingerprints, over a reference database (Chembl, v19) and the assignment of biological activity. It allows the identification of similar chemical compounds (analogues) to the input molecule. Hurakan compares the query molecule with the structures present in the reference database (Chembl v19) using Comparative Molecular Similarity Indices Analysis (CoMSIA) fields on a 3D grid. Molecules were compared according to the relationship with their environment using the 3D descriptors topologic surface area, lipophilicity, hydrogen bond donors/ acceptors count, and Van der Waals radii, thus obtaining biomimetic compounds with different chemical structures .[11]

Using DisGENET, a database that integrates information on gene–diseases associations, the targets obtained after the VP were related with the pathologies in which they can be involved. Thereafter, we filtered out the targets list, selecting only those related to neurodegenerative and cardiovascular disease.3D models of the selected targets were extracted from the Protein Data Bank (RCSB PDB). Then, the protein structures were modelling from them. For those without crystallographic structures available or showing poor sequence representation (<30%), homology models were constructed using SWISS-MODEL.The structures of the marine molecules were modelled from their 2D chemical structure.[12]

Toxicity was predicted using VEGA-QSAR and the T3DB database. VEGA-QSAR, integrating different QSAR models, is able to predict different toxicity endpoints, indicating the reliability of the prediction (ranging from 1 (low reliability) to 3 (high reliability) . To gain statistical significance and reliability, all the available models in VEGA were employed. Because of that, the results of each category were averaged over all the models used and then the results were classified according to its probability of being toxic in the following terms: no toxicity (0), low (<2), medium (2–2.75), or high (2.75–3)[13]. To complement the analysis performed with VEGA, the T3DB database was used. A 2D Tanimoto based similarity searching was performed over T3DB containing compounds, using the marine molecules as a seed. If the similarity was >0.65, the marine compounds were classified as toxic, if not as non-toxic.[14]

III. Conclusion:

Currently, except for the above-mentioned marine drugs that have been approved for clinical usage, there are many marine drug candidates that have been approved by several drug regulatory agencies worldwide for clinical studies at various stages; for example, Salinosporamide A (Marizomib/NPI-0052) for the treatment of malignant gliomas; Tetrodotoxin (TTX), a non-addictive analgesic for the treatment of advanced cancer, neuralgia, and vasculitis; Plitidepsin (Aplidine) for the treatment of multiple bone marrow ; and ASG-5ME for the treatment of pancreatic cancer etc. There are numerous kinds of marine organisms in the ocean, which thereupon produce countless special secondary metabolites. However, the current discovery of the active components in marine organisms is still at the beginning, and less than 1% of the total marine organisms have been systematically studied for their bioactive chemical compositions and corresponding mechanisms of action.
With the development of computer simulation technologies, molecular-docking-based technologies have become the direct methods to discover potential drug targets efficiently and on a large scale. At this point, the advantage of the molecular docking method is that all the molecules in the compound database are known compounds, and a considerable part of them can be easily purchased or synthesized according to the known synthetic route, and so the subsequent pharmacological tests can be conducted quickly. Moreover, it can simulate drug-receptor interactions, elucidate the mechanism of action of drugs, and increase accuracy, sensitivity, specificity, and predictability, which provides a good tool for drug research and development. In recent years, the development of computer technology, the rapid growth of target enzyme crystal structure data and algorithms, and the continuous updating of commercial small molecule databases have made molecular docking a huge success in drug design.

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