ROLE OF COMPUTER AIDED DRUG DESIGN IN MARINE DRUG DISCOVERY

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ABSTRACT

The term "drug design" refers to the process of developing new drugs with the aim of improving existing ones. Random screening of synthetic compounds, the synthesis of biologically active compounds based on naturally occurring drugs, the synthesis of structural analogues of naturally occurring lead molecules, and the application of the bioisosteric principle are only a few of the techniques that have been used. As a result, the most recent trend in drug development is to either completely reinvent a lead or optimise an established lead. The number of marine-derived items on the market has increased dramatically over the last decade. The sea is home to a diverse range of flora and fauna, the extracts of which have been shown to have therapeutic value in conditions such as cancer and macular degeneration. As a result, scientists are turning their attention away from synthetic substances and toward natural products. Drug production and testing, on the other hand, is a time-consuming operation. Researchers face obstacles at every stage of the process, from securing funding to obtaining good trial outcomes. Furthermore, due to global warming and human activities such as tourism and deforestation, the sea as a source is increasingly depleting. We've looked at a few promising marine compounds in this report. We've also included a few compounds that are currently being researched and may be beneficial to patients. This study also discusses the challenges that must be addressed in order to improve the success rate of marine drugs.

KEYWORDS

CADD, Marine Drug, Prototype, Analogues

INTRODUCTION

Computer aided drug design refers to all computer-assisted techniques used to discover, design, and optimise biologically active compounds with the potential to be used as drugs. The drug development process includes three pre-clinical stages before clinical trials: target selection, lead identification, and clinical candidate selection. Thanks to rapid advances in structural biology and computer technology, structure-based computer-aided drug design (CADD) using docking techniques, virtual screening and library design, as well as target/structure focusing combinatorial chemistry, has become a powerful tool in the multi-step process of drug growth.[1] By integrating current drug and disease expertise with inter-disciplinary contributions from other fields, CADD accelerates drug discovery. This procedure makes extensive use of statistical models and modelling approaches aimed at evaluating potential drug safety risks and planning new trials. Advances in software and hardware computational capacity and sophistication, as well as the identification of molecular targets and an expanding database of publicly accessible target protein structures, have allowed for rapid expansion in this field.[2]

CADD is being used to classify active drug candidates, pick leads, and optimise leads, that is, to convert biologically active compounds into appropriate drugs by enhancing their physicochemical, pharmaceutical, and ADMET/PK properties. The term biological target is widely used in pharmaceutical research to identify a native protein in the body whose function is altered by a drug, resulting in a desired therapeutic effect. The biological target is often known as a drug target in this context.[3] The following are the most popular drug targets for currently marketed drugs:

• DNA, Integrins, Miscellaneous

• Transporters

• Nuclear hormone receptors

• Nuclear hormone receptors

• Voltage-gated ion channels

• Ligand-gated ion channels

• Enzymes

MARINE DRUG

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.[4] 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. It identifies the challenges that must be overcome in the pursuit of marine drug testing, as well as potential solutions. It also emphasises the significance of preserving this vital resource.[10]

DISCOVERY OF MARINE DRUG

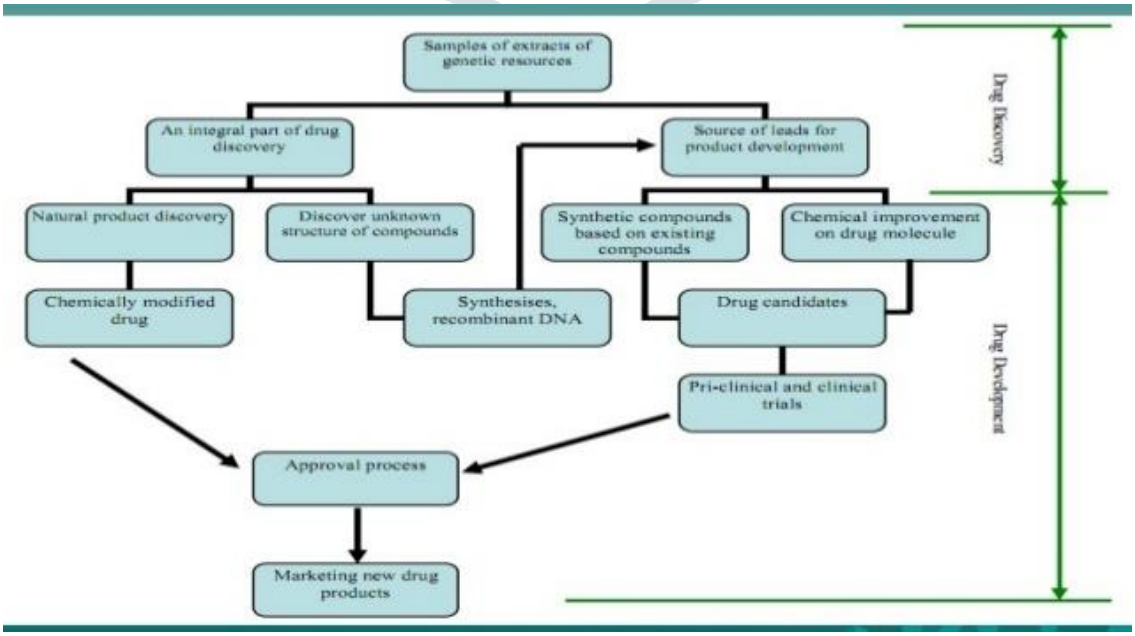

Fig. Marine Drug Discovery and Development

STAGES OF NEW DRUG DEVELOPMENT

- Identifying natural/marine products
- Identifying chemically modified drugs
- Identifying substances of unknown structures
- Recombinant DNA, synthesis
- Source of product creation leads
- Compounds that are synthesised from existing compounds
- Improvements to the drug molecule's chemical composition
- Candidate drugs
- Trials in the preclinical and clinical stages
- Approval procedure
- promoting new pharmaceuticals [20]

DRUGS CURRENTLY UNDER TRIALS

- Aplidine
- Bryostatin-1
- Kahalalide F
- Plinabulin
- Cytarabine
- Dolastatins
- Ectenaisdin 743 (ET-743)/Trabectedine/Yondelis
- Squalamine
- Pseudopterosins and Seco – pseudopterosins
- Eribulin mesylate
- Cortistatin
- Thiocoraline

A. APLIDINE-

Source-

Aplidine Source is a second-generation didemnin obtained from Mediterranean tunicate aplidium albicans, also known as dihydrodemnin B.[11]

Mechanism of action (MOA)-

It activates the epidermal growth factor receptor, the Src nonreceptor protein tyrosine kinase, and the c-Jun NH2-terminal kinase and p38 mitogen-activated protein kinase serine threonine kinase. Glutathione homeostasis is disrupted. Apoptosis is induced as a result of both of these activities.[11] It causes G1 arrest as well as G2 blockage. [12] It stops tumours from growing by inhibiting the enzyme ornithine descarboxylase. It inhibits the expression of the vascular endothelial growth factor gene, which has an antiangiogenic effect.[12] The levels of expression of the cyclin-dependent kinase inhibitor p27kip1(p27) by particular short hairpin RNA correlate inversely with Aplidine sensitivity[10].

Trials-

Trials are currently underway for the treatment of multiple myeloma.[8] It is currently being tested in a phase 2 trial for the treatment of primary myelofibrosis, post-polycythemia vera myelofibrosis, and solid tumors.[11] For the treatment of acute lymphoblastic leukaemia and multiple myeloma, it has been designated as an orphan drug.[10]

Adverse drug reactions (ADR) –

Toxicities include muscular atrophy and the loss of thick myosin filaments, in addition to hypersensitivity, nausea, transient transaminitis, and other symptoms. The use of L-carnitine, on the other hand, can help to alleviate this.[10]

B. BRYOSTATIN-1

Source-

Bryostatin-1 is a macrocyclic lactone isolated from Bugula neritine, a marine invertebrate.[11]

Mechanism of action (MOA)-

Bryostatin-1 is a powerful activator of protein kinase C (PKC), inhibits the synthesis of matrix metalloproteinases, and antagonises tumor-promoting phorbol esters. It induces myeloid and lymphoid cell differentiation, platelet aggregation, and promotes hematopoiesis , modulates bcl-2 and p53 gene expression, and induces apoptosis by downregulating multidrug-resistance 1 (MDR1) gene expression. It also has immunomodulatory functions.[11]

Trials-

It is currently being tested in a phase II trial for non-lymphoma Hodgkin's and chronic lymphocytic leukaemia. Upregulation of CD11c/CD22 coexpression on CD20+ B cells is thought to be its mode of action.[13] It is being tested in patients with metastatic renal carcinoma and soft tissue sarcoma in a phase I trial in combination with temsirolimus .[14]

Adverse drug reactions (ADR) –

Bryostatin-1's dose-limiting toxicity (DLT) has always been extreme myalgias, which were dose-related, cumulative, and independent of the administration schedule. Patients who were given doses that were higher than the maximum tolerated dose had a large drop in platelets, leukocytes, and, in particular, neutrophils haemoglobin levels in the days following surgery. However, there was no effect on bone marrow progenitors. Hence it was thought to be due to peripheral blood cells pooling. These elevations typically recovered to baseline shortly after treatment, with the exception of haemoglobin, a decrement which persisted 1–2 weeks after dosing.[11]

New studies-

It is currently being researched as a cure for Alzheimer's disease. It works by activating PKC, lowering protein A, and restoring synapses that have been lost.[10] It can also be used to treat HIV because it activates PKC, reduces CD4/CXCR4 expression, and allows latent virus to be removed from cellular reservoirs such as the brain and lymphoid organs.[10]

C. KAHALALIDE F

Source-

Elysia rufescens, an Indopacific mollusk, provides it.[15]

Mechanism of action (MOA)-

It results in the loss of mitochondrial membrane potential and lysosomal integrity, as well as extreme cytoplasmic swelling and vacuolization, abnormal chromatin clumping within the cell nucleus, and cell death. Elisidepsin is a Kahalalide F family cyclic peptide derived from synthetic marine sources. It is more active in epithelial cells with high E-cadherin expression and low vimentin expression.[16]

Trials-

It is currently being tested in a phase II trial for non-small cell lung cancer. Elisidepsin is currently being tested in a phase Ib/II trial for the treatment of esophageal and gastric cancer that is locally advanced or metastatic.[10]

Adverse drug reactions (ADR) –

Consequences include a non-cumulative increase inALT/AST transaminases and gamma-glutamyltransferase (GGT).[17]

Studies-

It has antileishmanial properties. It changes the situation. The parasite's plasma membrane decreases intracellular ATP and has the benefit of being less susceptible to resistance production Its analogues are being researched for the future.[10] Psoriasis treatment, pancreatic carcinoma treatment, and hepatocellular carcinoma treatment carcinoma, melanoma, breast cancer, and prostatic carcinoma are examples of cancers.[17]

D. PLINABULIN-

Source-

Plinabulin is a synthetic analogue of phenylahistin (halimide), a diketopiperazine found in marine and terrestrial Aspergillus sp.

Mechanism of action (MOA)-

Plinabulin inhibits cell proliferation and endothelial cell tubule development, causing tumour vascular endothelial cells to be disrupted. Tumor necrosis results as a result of this. Plinabulin-induced apoptosis in tumour cells is mediated by caspase-3, caspase-8, caspase-9, and cleavage of poly

(ADPribose) polymerase. Furthermore, as a primary target, plinabulin causes phosphorylation of the stress response protein JNK. Plinabulin is a protein that blocks cells in metaphase in an abnormal manner. Alignment of chromosomes It interferes with the formation of In proliferating tumour cells, microtubules and microfilaments cause mitotic arrest.[10]

Trials-

A phase 1 study of plinabulin as a single agent in patients with advanced malignancies (lung, prostrate, and colon cancers) revealed a favourable pharmacokinetic, pharmacodynamic, and safety profile; a phase 2 study of plinabulin in combination with docetaxel in patients with non–small cell lung cancer revealed promising safety, pharmacokinetic, and efficacy results.[10]

Studies-

It caused cell death in patient multiple myeloma cells while leaving normal mononuclear cells unaffected.[18]

Adverse drug reactions (ADR) –

It triggers a temporary rise in blood pressure. Infusion reaction (bradycardia with syncope), myocardial infarction, vomiting, confusion, and pain were among the serious side effects. The temporary changes in blood pressure or emesis caused by plinabulin was due to an infusion reaction rather than an allergic reaction. Even if significant emesis is present, it can be regulated with antiemetics. Tumor pain is thought to be caused by structural and pain mediator effects on surrounding tissues caused by plinabulin-induced tumour necrosis, and is well controlled with analgesics and/or improves with continued care. Apart from the temporary changes in blood pressure and heart rate mentioned above , intense cardiac testing revealed that plinabulin has no effect on cardiac function.[19]

CONCLUSION

This article provides an overview of marine drugs that have curative potential and are currently being tested in clinical trials. It also aims to highlight a few compounds that can be further optimised to yield positive results. Obtaining and producing marine medicines, on the other hand, is fraught with difficulties. It's also important to consider the financial aspect. Furthermore, due to human degradation, this resource is rapidly depleting. This analysis attempts to explain the roadblocks in this endeavour and offers critical ideas that could help in this rapidly growing field of study.

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