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Recent Trends in Novel Marine Pharmaceuticals: an Overview

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Abstract

The growing burden of disease and treatment failures drive the need for new drug discovery. The potential exploitation of natural resources across land and water paves the way for future major innovations in drug discovery*. The marine biosphere is the largest on earth and is home to a vast array of organisms. Inhabited. Living conditions are fundamentally different from the terrestrial environment. The production of certain secondary metabolites is vital for adaptive mechanism for marine organisms to survive in the sea. These metabolites have interesting biological activities as potential pharmaceuticals for humans. It also provides ecological resources including various aquatic plants* and animals.

Drugs of diverse resource from marine environment aids to combat major diseases such as malaria or cancer. These aquatic organisms have been studied for their antibacterial, immuno-modulatory, antifungal, anti-inflammatory, anticancer, antibacterial, Neuro-protective, analgesic, and anti-malarial properties. They are widely used worldwide for the development of new drugs*. The marine environment, with its scaffolding with remarkable features, has fascinated scientists and generated a great deal of interest in searching for new compounds. Sponges, algae, tunicates, sea whips, etc. from marine pipelines are important sources of biological agents. Recent technological advances have further expanded the field of drug discovery in the isolation and evaluation of marine*-derived products

*Keywords:****Ecological Resources, Innovations, Terrestrial, Technological Advances.***

1. INTRODUCTION

Many chemicals and products made from algae are economically important and are widely used algae as a source of fibre, minerals, antioxidants, vitamins, pigments, steroids, lectins, halogenated compounds, polyketides, polysaccharides, mycosporine-like amino acids, proteins, polyunsaturated fatty acids and other lipids; henceforth , they are largely consumed in many countries. Further, isolated compounds, extracts and fractioned extracts have been reported to yield important biological activities, including anti-inflammatory, leishmanicidal, reduction in triglyceride levels in the liver and serum, for the treatment of Leprosy, as well as for their trypanocidal, antioxidant, anticancer and microbicidal properties .Therefore, many studies have been published, and many patents for chemicals extracted from marine algae have been registered for human health and nutrition. Due to the various uses and wide availability of the photosynthetic organisms, the interest has shifted from wild harvest to farming and controlled cultivation. The compounds isolated from marine algae have sophisticated chemical structures, and some have shown great potential in the pharmaceutical and medical areas, including drugs for neglected tropical diseases (NTD)

The importance of natural products (NPs) in drug discovery has been extensively documented, which includes their contribution to the development of present drugs. The NP chemical diversity is more closely aligned with drugs than synthetic libraries, hence making them ideal candidates for drug discovery projects. Marine creatures can be considered the very recently discovered source of bioactive natural products compared to terrestrial plants and non-marine microorganisms. Their exploitation is mainly dependent on the development of sample collection techniques and improvements in spectroscopic analysis, primarily NMR and separation methods. By the end of 2016, approximately 28,500 marine natural products (MNPs) had been identified. Given the ecological role of MNPs as

chemoprevention, this is not surprising. The fact that NIH/NCI is the primary source of funding for MNP drug research in the United States has been suggested by some authors as a major reason for the greater emphasis on antitumor activity.[1-6]

2. HISTORY

The oceans cover over 70% of the earth's surface and are home to a huge variety of species. The first living organism found in the sea was more than 3500 million years ago, and as a result they have a very large revolutionary period. There are 35 taxonomically identified animal phyla, 34 are found in marine environments, and many of these are found exclusively in marine media. Over time, harsh ocean conditions favoured the production of a wide variety of molecules with unique structures in terms of diversity, structural and functional characteristics, and also compared to NPs from terrestrial organisms. This is due to the large number of yet unknown scaffolds discovered, given the structural diversity of MNPs and the fact that less than 5% of the deep sea has been explored. In most cases very small amounts.

Total chemical synthesis or semi-synthesis is the most useful technique to solve this supply problem. Alternatively, in some cases biotechnology techniques can be used for Large-scale fermentation or invertebrate culture of the producing microorganism, despite being difficult than the conventional methods. [7]

In hindsight, it is difficult to determine whether inhibition is due to antibiotic producers or microbial predators, given the current perception of dormancy/diapause, it was found that the researchers inadvertently stumbled upon the concept of non-cultivable antibiotics. However, it is impossible to dispute the observations of the last century, as it was continued to be credited for the original work on marine bacteria that inhibit other organisms. The given explosive prosperity of several scientific disciplines in the 19th and 20th centuries, was a long hiatus before further research on microbial control in the marine environment began.

Thus, it became increasingly clear that something in seawater was indeed bactericidal against non-marine bacteria .Such early researchers found that bacteria, especially those from the gut, declined rapidly in number when added to seawater. Subsequently, a commendable study was published that ushered in an era of research on the antagonistic interactions of microorganisms in the marine environment [3, 8]

2.1 Exceptional Nature of Marine Floral Drugs

Marine flora is inclusive of micro flora (bacteria, actinobacteria, cyanobacteria and fungi) microalgae, macro algae (seaweeds) and flowering plants (mangroves and other halophytes). The ocean covers almost 71% of the Earth's surface and is rich in biodiversity, with microbiota and microalgae alone accounting for over 90% of marine biomass. This vast marine floral resource will offer a great scope for discovery of new drugs. It is increasingly recognized that ocean contains a huge number of natural products and novel chemical entities with unique biological activities that may be useful in finding the potential drugs with greater efficacy and specificity for the treatment of human diseases It cannot be denied that with 3.5 billion years of existence on earth and experience in biosynthesis, the marine micro floras remain nature’s best source of chemicals. The marine organisms produce novel chemicals to withstand extreme variations in pressure, salinity, temperature, and so forth, prevailing in their environment, and the chemicals produced are unique in diversity, structural, and functional features [9-11]

3. CLASSIFICATON OF MARINE DRUGS

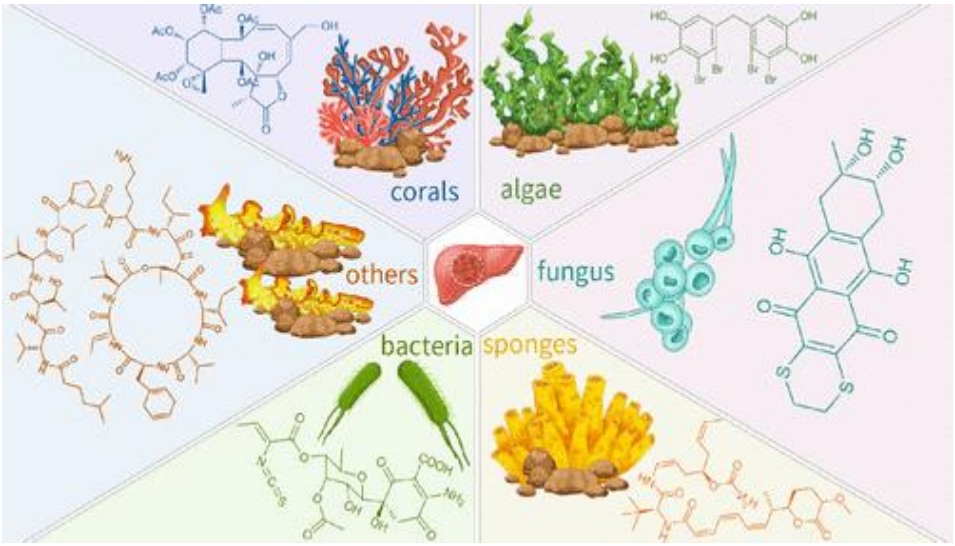

Fig-1 Classification of marine drugs [12]

For systematic analysis of drugs derived from marine organism, the drugs have been divided in these subtopics:

- Marine microorganism
- Marine algae and plants
- Marine invertebrates
- Marine bacteria
- Marine sponge
- Marine fungi
- Seaweeds
- Squalamine
- Marine functional food
- Lipids

3.1 Marine Microorganism

Marine bacteria Pseudoalteromonas produce toxic proteins, ployanionicexopolycahharides, substituted phenolic, and pyrolle containing alkaloids, cyclic peptides and a range of bromine-substituted compounds. These biomaterials showed antimicrobial, anti-fouling, algicidal and various pharmaceutically-related activities [13-16]

3.2 Marine algae

Marine algae are the source of many bioactive compounds with antioxidant activity. Both microalgae and macroalgae contain pharmacologically active compounds. These biologically obtained materials are used in cosmetics and pharmaceuticalsScientists have evaluated the mechanism of action, disinfection, efficacy and potential uses of products derived from red, brown and green algae in the laboratory[16]

3.3 Marine Invertebrates

Marine Invertebrates produce their own chemical compounds in their environment to protect themselves from predators. These secondary metabolites are now recognized as powerful medicines to

cure disease. Some, such as Prialt (Ziconotide; a powerful analgesic) and Yondelis (Trabectedin or ET-743; antineoplastic agent), are already on the market and others are in clinical trials. E.g. Alpidine and Kahalalide.

Asians are familiar with the traditional medicinal uses of sea cucumbers. They have long used sea cucumber as a dietary supplement. The major secondary metabolites of sea cucumber are triterpeneglycosides .Sea cucumber (Holothuriascabra) is processed to make high-protein biscuits and jams [16-17]

3.4 Marine bacteria

Marine bacteria mainly marine bacteria are discussed for their growth in response to seawater requirements or sodium in particular. Screening marine bacteria isolated from the surface of invertebrates and seaweeds showed that the majority of bacteria produced antimicrobial metabolites. In 1996, the first antibiotics were produced by marine bacteria. In addition, the bacteria that live in biofilms (formed on the surface of marine microorganisms) contain a greater proportion of antibiotic-producing bacteria than any other marine environment. [17]

3.5 Sponges

Sponges (Phylum: Porifera) form one of the most primitive multicellular organisms (>600 million years old) on Earth. Due to their long evolutionary history, these organisms have great genetic diversity and produce several new metabolites with potential biomedical applications.

During the last 35 years, much attention has been paid to the secondary metabolites of many marine organisms. Novel and structurally distinct secondary metabolites have been isolated and recognized from marine microorganisms. As a result of this struggle, many compounds were developed using new chemical models and launched in 2004, while most other candidates are in clinical trials. Lineages and candidate phyla have proven to be milestones through the discovery of phylogenetic complexes. Microorganisms are in many ways more accessible than those in seawater, opening unique research horizons. Most sponges act as microbial fermenters, opening exciting new avenues in marine microbiology and biotechnology [18-21]

3.6Marine fungi

Marine fungi derived from marine fungi a large number of compounds are in clinical use today. It also contains sorbicillacton A, This compound is extracted from a fungus associated with sea sponges and represents an advanced stage of development for its treatment. It produces antioxidant compounds such as 4, 5, 6-trihydroxymethylphthalide from and from Epichoum sp. These antioxidants prevent oxidative damage associated with diseases such as dementia, atherosclerosis, and cancer. [21]

3.7Sea weeds

Sea weeds are those minerals which hold a great priceand arefound in sea.

3.8 Squalamine

Squalamine comes from the liver of the dog shark, it is used in cancer and diabetic retinopathy. It is a geranyl phenazine-diol anti-cholinesterase inhibitor (Streptomyces isolator).Fucoidan derived from focus vesiculosus may be new pharmaceutical compound in the treatment of ovarian cancer. Arthrinium marine fungus is used to treat prostate cancer, lines - PC 3 assay. Sea cucumber which is a tegument extract is used as anti-viral to treat human rota virus. Octopus vulgaris derived from taurine rich in water soluble extract is hepato-protective by regulating BCL 2 signalling. [1]

3.9Marine Functional Foods The marine environment is chemically and biologically very diverse. Many materials derived from the marine environment have been used as foods and food ingredients. The most common are alginate, marine polysaccharides, carrageenan and agar. [21-24]

3.10 Lipids from marine sources are prime targets for lipid extraction due to their unique lipid composition compared to terrestrial sources. The fatty acid composition of marine species is typically

characterized by a relatively high proportion of PUFAs, a significant amount of monounsaturated fatty acids, and a low content of saturated fatty acids there are two classes of PUFAs, ω3 and ω6, distinguished by the position of the first double bond at the methyl end of the fatty acid [25-26]

4. MARINE DRUG ACTIVITY

4.1 Chemotherapy

Oceans cover more than 70% of the planet Total global biodiversity is estimated to be about 500 × 106 species of prokaryotes and eukaryotes The marine environment actually contains nearly 250,000 It is a reservoir of highly diverse life with species described [27,28]. Among marine organisms, 3.7 × 1030 microorganisms have been found in the marine environment [29], and although 99% of all bacteria cannot be cultured, they synthesize many attractive natural products that are potential drug candidates. [30]. this unusual chemical and pharmacological range of marine organisms may result from their need to produce secondary metabolites as defence tools to survive in extreme environments. Resists temperature, salinity, pressure and predators. Marine plants have been used medicinally all over the world since ancient times, including in India, China, the Middle East, and Europe [31]. Since then, less than 5% of the deep sea has been explored and less than 0.01% of the deep seafloor has been sampled in detail [32]. The Caribbean sponge (Cryptotethyacrypta) was the first marine organism to be chemically studied in detail [33], and prior to the identification of cytosine arabinoside (ara-C) in 1950-1960, the Extensive phytochemical studies have been conducted on the compounds [34-36]. In addition, micro-biota (bacteria, actinomycetes, cyanobacteria, fungi), microalgae, macro algae (algae) [31], invertebrates [37,38] sponges, soft corals, nudibranchs, lumpfish, nudibranchs, bryozoans, etc. marine organisms, such as tunicates , have been studied to fight cancer [39,40]The effects of bioactive molecules have been studied in clinical studies in various types of cancer [41-45]. Moreover, new tools have been adopted as advances in marine chemistry continue. B. Metabolomics to study various aspects of seafood [27-45].

4.2Leishmaniasis

Leishmaniasis is caused by more than 20 Leishmania species and is transmitted to humans through the bites of infected phlebotomycins and flies. The disease has a wide range of clinical manifestations, including those of cutaneous, mucocutaneous, or visceral leishmaniasis. In the Old World (Africa, Europe, Asia), cutaneous leishmaniasis (CL) is caused by Leishmania major, L. Some zymogens of tropics, L. aethiopica and L. Infantum. Primarily in the Latin American New World, the etiologic species involved is Leishmaniabrasiliensis, the most widespread species, followed by L. amazonensis, L. Guyanensis and L. panamensisLeishmaniamexicana、L. pifanoi、L. venezuelensis、L. peruviana、L. Shawi、L. lainsoni, found mainly in the Amazon and Central America, may also be associated with CL. Leishmaniadonovani, a viscera-tropic Old World species, can cause CL during or after visceral leishmaniasis (VL), known as post-kala-azar cutaneous leishmaniasis. Muco-cutaneousleishmaniasis (ML) affects the mucous membranes of the nose and oral cavity and causes L. brasiliensis, L. panamensis, L. Guyanensis and L. amazonensis in the New World and L. major and L. Infantum in the Old World [48]. VL is caused by L.donovani in Asia and Africa, and L. Infantum, formerly known as L. chagasi, in southern Europe and South America. While CL tends to resolve on its own, ML causes severe facial deformity and VL is fatal if left untreated, causing an estimated 59,000 deaths annually worldwide [47, 6]

4.3Anti-alzhimers

Anti-Alzheimers activity was found in the compounds such as Bryostatin-1 & DMXB-A which is extracted from Ectoprocta (species-bugulaneritina) which is a synthetic analogue of the toxic alkaloids which are produced by nemertines worm species such as paranemans peregrine and amphiporuslactifloreu which acts by enhancing the cognition and sensory deficit. Currently, these compounds are under phase II and not released into the market. [49]

4.4 Anti-Biosis

Rosenfeld &ZoBell (1947) were the first ones to carryout systematic antibiotic study of marine organisms against a serious human pathogen B. Anthracite. A total of 58 pure cultures of marine bacteria come from the collection of Dr. C.E. ZoBell, ZoBell&Upham (1944). They were maintained in a nutrient-rich medium

containing peptone and yeast extract prepared in an aged seawater base (pH 7.4). To assess the presence of inhibitory activity, these investigators used the pore plate method of pouring chilled agar seeded with pathogen cultures into Petri dishes. After solidification, this medium was streaked with a pure culture of marine bacteria.

Inhibition was indicated after incubation by the presence of clear zones in the pathogen confluent lawn. The main antagonists were representatives of the genera Actinomycetes, Bacillus, Micrococcus and Serratia, but there were no strains named Achromobacter, Flavobacterium, Pseudomonas, Sarcina, and Vibrio. In particular, B. anthracis. Therefore, antibiotics were recovered on nutrient-rich agar medium supplemented with 0.0000001% (w/v) vitamin B. The incubation of the inoculated was done at 30 °C for 3 days (apparently this temperature was above the optimum temperature for his Ps. bromutilis), after which the colonies were removed by scraping and subjected to chemical extraction. It was stored at -15 °C for a methanol-ethyl ether-chloroform regimen was used to extract the antibiotics [48]

4.5 Analgesic

Tetrodoxin, a compound isolated from fish, algae and bacteria blocks voltage dependent sodium channels and is being tested for phase III for neuropathic pain in cancer patients and peripheral neuralgia in cancer patients respectively [49]

4.6 Anti-fungal activity

This was found in sponges obtained from p.vesiculosa beta –carboline which is a peptide and works on mechanism of activation of 1, 3-beta-D-glucan synthesis [50]

This activity was also found in another species of sponge called theonellamide F which is a peptide and has MDR 1 efflux pump inhibition. [51]

4.7 Anti-malarial activity

This was found in the sponge batzelladine alkaloids and homogentisic acid with the main constituents being alkaloid and shikmate respectively and it works on the mechanism of inhibition of Pfnek-1 enzyme. [49]

4.8 Anti Protozoal activity

This was detected in C.cervicornisditerpene and alga agelasine analogues which is mainly constituted of terpene and acts by mitochondrial swelling and damage. [49]

4.9 Anti-viral activity

was found in alkaloids such as coral manzanie A , sponge xiamycine& bacterium beaculiferins and these acts by the mechanism ; Early ICPO gene transcription inhibition, Selective inhibition of CCRS tropic HIV , Binding to Vif-APOBEC3G and gp41 respectively. And these are mainly used for the inhibition of HIV-1 infection. [49-51]

4.10 Use of marine compounds in diagnosis and experimental tools

The marine compound (isolate) is used as a diagnostic, disease modifying and laboratory tool. Pfu, an enzyme from the marine thermophilic*Pyrococcus furiosus* used for PCR. GFP, green fluorescent protein isolated from the jellyfish *Aequorea Victoria*. It is used as a biological marker to label cellular structures in vitro and in vivo. Shimomura (Japan), Chalfie and Tsien(USA) received the Nobel Prize in 2008 for their discovery and applications in the year 2008. LAL-Limulus amebocyte lysate obtained from Polyphemus crab, for detection of pyrogenic lipopolysaccharidein bacteria. Keyhole lymph hemocyanin (KLH) is a largemulti-subunit oxygen-transporting metalo-protein found in the hemo-lymph of the giant lymph of Megathura crenulata, a marine mollusc native to the California coast of the United States. [1]

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5. MERITS AND DEMERITS OF MARINE PHARMACEUTICALS

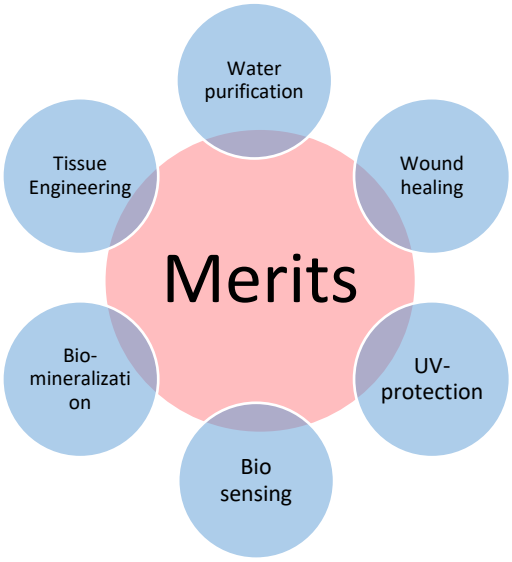

Figure 2-Merits of Marine Pharmaceuticals

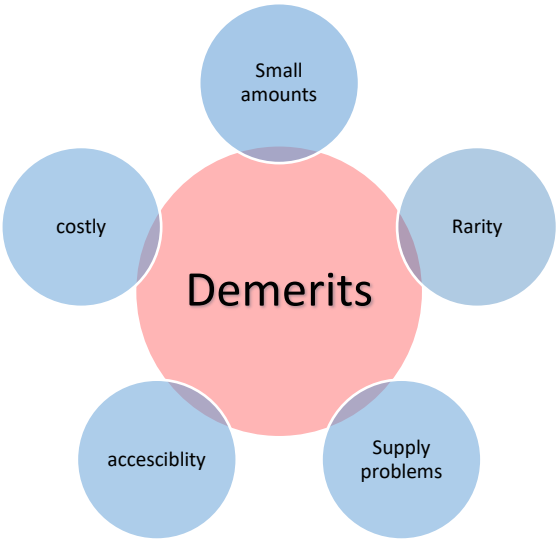

Figure 3-Demerits of Marine Pharmaceuticals

CONCLUSION

Although soil-derived drugs are incredibly vital for human humanity, is not enough to satisfy the needs. The oceans due to its vast space coverage around the world makes it easy for obtaining resources ,makes it feasible and they have high potential for future developments in drug development. The rich diversity of marine biological data, with its unique physiological adaptations to the harsh marine environment provides a fertile source for the discovery of life-saving drugs.

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