Potent bioactive compounds from the ocean: some interesting aspects and applications

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ABSTRACT

Over seventy percent of the earth's surface is covered by oceans, and it is an established fact now, that life originated in the oceans. Additionally, the oceans are also the source of matchless natural products that are mainly accumulated in living organisms. Several bioactive compounds of therapeutic interest have been isolated from marine invertebrates, and some of them have been reported to be of microbial origin. Numerous of these compounds show pharmacological activities and are helpful for the invention and discovery of bioactive compounds, primarily for deadly diseases like cancer, acquired immuno-deficiency syndrome, etc., while others have also been shown to possess several valuable properties. The secondary metabolites of microorganisms, algae and invertebrates, possess lifesaving properties, and are deadly toxins as well, depending on the dosage. The useful applications of these compounds, as bio-markers is also being explored, to further enrich pharmacological information. Recent developments have opened colossal areas of research for the isolation of biologically active compounds from marine flora and fauna.

Key Words: Marine natural products, seas, wonder drugs, marine invertebrates, bioactive secondary metabolites, fatal toxicity, bio-marker compounds, oceanic biodiversity.

INTRODUCTION

It is an undisputable fact that the development of drugs has greatly improved the quality and duration of human life. Chemical compounds, such as morphine, quinine, penicillin, streptomycin, reserpine, curare alkaloids, and digitalis, etc., led to treatments and even complete cures for diseases that were earlier considered to be fatal. The process of drug discovery continues today at a pace greater than ever before, and although sophisticated new approaches are used, nature continues to provide the biochemical insight forming the foundation of many newly developed drugs. One example is the recently approved anticancer drug taxol, a compound extracted from the bark of the North American Yew tree. Taxol, perhaps by virtue of its unique mechanism of action, has shown excellent results in treating several forms of cancer that were previously difficult to treat. Disappointingly, many of the "wonder drugs" generated over the past several decades have become less useful due to the development of drug resistance. Many pathogenic bacteria, once susceptible to antibiotics, have developed sophisticated biochemical methods to escape the effects of these drugs. A strain of drug-resistant mycobacterium, the pathogen that causes tuberculosis, for example, is almost totally resistant to our arsenal of antibiotic drugs. Some infections are, today, produced by bacteria that are immune to all known antibiotics. Similarly, some forms of cancer have evolved multiple drug resistance, making virtually all drug treatments ineffective.

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Global marine drug discovery scenario

Drug discovery efforts today, include the inhabitants of the world's oceans as a new source of biodiversity and novel drugs. In contrast to the terrestrial environment, little ethnomedicinal information is available to guide current marine research. With the exemption possibly of southern China, few societies have used marine organisms as crude drugs. Thus studies now in progress have relied on ecological observations of chemical defense and survival to identify those organisms that might be expected to contain drug candidates. Pharmacological investigations of oceanic organisms are relatively new and have been based on the establishment of unprecedented "scientific bridges" between the marine and pharmaceutical sciences. In this day and age, roughly one-half of all cancer drug discovery focuses

on marine organisms, and forecasts for the future are brilliant, as well. In fact, some of the most important recent discoveries have been from the oceanic milieu. Marine drug discovery began in the late 1970s by early investigators demonstrating unequivocally, that marine plants and animals were genetically and biochemically unique. Over 18,000 structurally unique and often highly bioactive metabolites have now been isolated from marine plants and animals. After the uniqueness of marine metabolism became accepted, programs began to evolve that linked academic marine scientists with biomedical researchers in the pharmaceutical industries. Programs, which established the foundations of today's efforts, were created in the 1980s in the United States, in Japan, and in Australia. Today these programs are expanding on the basis of their continuing discoveries of novel new drug leads. Unlike the majority of terrestrial drug research, marine drug discovery programs have been applied to selected, difficult to treat diseases that have eluded cures for decades. Yet, progress has been observed in many of these difficult areas. New drug leads have been identified with potent immunosuppressant properties, with anti-inflammatory properties, and with significant anticancer potential[1-2]. Perhaps the first molecule discovered was the unique cyclic ester bryostatin 1 isolated and defined by researchers at Arizona State University. Bryostatin 1 occurs as a trace component of the common bryozoan *Bugula neritina,* which occurs worldwide often as a conspicuous component of the fouling communities on pier pilings. The molecule was the most selective antileukemia agent, and recognized as a very potent inhibitor of numerous leukemia cells in culture. As is regularly the case, only selected populations of this illustrious animal were found to contain bryostatin 1. Bryostatin 1 has already been acknowledged as a chemically and pharmacologically exceptional molecule of great interest in basic medical research[3]. This compound possesses unprecedented immunostimulatory properties, and it activates protein kinase C, an important regulator of hormone-mediated signal transduction, and a novel enzyme target for the development of new antitumor drugs[4]. In the 1970's, as part of an NCI-sponsored survey of Caribbean invertebrates, the impressive cytotoxic properties of extracts of the mangrove ascidian *Ecteinascidia turbinata* were discovered. Although it was clear, even then, that this animal contained substances of great importance, the difficulty encountered in isolating and identifying the active substance(s) rendered this project virtually unsolvable, due to the fact that active substances were present in vanishingly small amounts, and the compounds were apparently of a very new and difficult to isolate structural class. After 20 years of advancements in chemistry, the active substances, named the ecteinascidins, were isolated and described by researchers at the University of Illinois and the Harbor Branch Oceanographic Institution[5]. The most abundant compound, Ecteinascidin 743, showed excellent potency, IC_{50}, = 0.5 ng/ml against murine (L-1210) leukemia *in vitro* and significantly extended the life spans of mice infected with P-388 lymphocytic leukemia. In subsequent testing, this compound showed selectivity towards MXI human mammary tumors cultivated in mice. Unlike bryostatin 1, ecteinascidin 743 is chemically related to a rare group of microbial antibiotics, the saframycins, which has raised the question of a possible microbial source existing within the tissues of this ascidian[6]. Another Caribbean ascidian, *Tridemnum solidum,* has also been recognized to contain substances of potential use in cancer chemotherapy. This ascidian was found to contain a series of cyclic peptides, the Didemnins, all of which were closely related. The most medicinally important of these compounds, Didemnin B, showed impressive cytotoxicity against lymphomas and significantly extended the survival of mice in the P-388 leukemia assay. On the basis of these encouraging properties, a large-scale collection of this animal was undertaken and larger amounts of Didemnin B were isolated[7]. Unfortunately, Didemnin B has subsequently been found to exhibit significant toxicity at doses near those required for life conservation. It is important to point out, however, that the evaluation of new drugs is a complex process in which both negative and positive results are continuously evaluated over time. Taxol, for example, required over 20 years of study before it was approved as a cancer drug. This fact has been once again realized during the development of Didemnin B. A more recent addition to the list of thrilling marine anticancer agents is dolastatin 10, a linear peptide discovered by researchers at Arizona State University from the sea hare *Dolabella auricularia*, collected in the Indian Ocean. Found in complex mixtures with related peptides, dolastatin 10 showed outstanding inhibitory effects against several forms of skin cancers in laboratory, studies. More importantly, subsequent whole animal testing showed this peptide to provide significant effects in controlling human melanoma in implanted mice[8]. The element of curiosity in this work is the true origins of the peptides in *D. auricularia.* Sea hares are most often herbivores, and it has been unequivocally demonstrated that these shell-less mollusks acquire defensive chemicals from their diets rather than synthesizing them as many animals do. Thus Dolastatin 10 and its analogs are most likely of an algal dietary origin. Based on our knowledge of the chemistry of marine algae, the Dolastatins are likely to be produced by filamentous blue-green algae (cyanobacteria), which are often abundant in these habitats.

Many of these compounds have possessed important biomedical properties, but only recently was a sponge-derived compound, halichondrin B, added to the list of agents to enter clinical trials. Halichondrin B, a novel polyether, was isolated and first identified in Japan. This remarkable metabolite was discovered in the sponge *Halichondria okadai*, various collections of which have yielded a variety of diverse toxins. Halichondrin B is a novel