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Review

Potent anticancer compounds from the ocean

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Over 70% 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. Recent developments have opened colossal areas of research for the isolation of biologically active compounds from marine flora and fauna.

Key words: Chemical compounds, seas, wonder drugs, marine invertebrates, secondary metabolites, 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. Deplorably, 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.

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

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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 (Marinlit, 2007; Proksch and Müller, 2006). 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 (Pettit, 1982). 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 (Suffness et al., 1989). 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 (Wright et al., 1990). 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. On the basis of these early studies, and more recent advanced preclinical investigations, ecteinascidin 743 will soon begin clinical trials in Europe. 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 (Rinehart et al., 1990). 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 (Rinehart Jr. et al 1981). 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 (Pettit et al., 1987). An inquisitiveness of 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 synthesi-

sizing 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 compound, related most closely to several of the toxins produced by toxigenic dinoflagellates (Hirata and Uemura, 1986). Due to this relationship and for the reason that *H. okadai* had been found to concentrate okadaic acid, a metabolite of the dinoflagellate *Prorocentrum lima*, it seems logical that the compound may also be of dinoflagellate origin probably acquired by the filter feeding process. Sustaining this concept, Halichondrin B has recently been isolated by several investigators from a variety of sponges. Halichondrin B shows selective antitumor effects against human ovarian cancers in mice, as well as activity against melanoma and various forms of leukemia. It seems clear that Halichondrin B is one of the most promising new anticancer drugs isolated to date. Another example of molecules being intensely studied are discodermolide, a unique immunosuppressive and cytotoxic agent, isolated by Harbor Branch Oceanographic Institution scientists from the deep water sponge *Discodermia dissoluta* (Gunasekera et al., 1990), and curacin, a novel anti-cancer agent from the Caribbean bluegreen alga *Lyngbya majuscula,* discovered by researchers at Oregon State University (Gerwick et al., 1994). Discodermolide has been shown to possess the identical tubulin polymer stabilizing properties as taxol, which certainly indicates that comprehensive preclinical studies should be undertaken (Haar et al., 1996). Among recent discoveries of significance, Sebastianines A and B, two novel pyridoacridine alkaloids with fresh ring systems, have been isolated from the tunicate *Cystodytes dellechiajai* (Torres et al., 2002), and a novel cytotoxic 16-membered macrodiolide, Amphidinolide X, has been isolated from a marine dinoflagellate *Amphidinium* sp (Tsuda et al., 2003).

SETBACKS: THE TOXICITY FACTOR

As these compounds are cytotoxic, they inherently possess fatally toxic properties, on several instances. As a result, in due course, some of them were prematurely withdrawn from the clinical trials due to life-threatening toxic side effects in the patients. Didemnin B has shown ineffectiveness to moderate anticancer response in different target sites and always invariably accompanied with high toxicity to the patients (Kucuk et al., 2000). However, ultimately due to its extreme toxicity, it was withdrawn from the phase II clinical trials (Amador et al., 2003). Moreover, Dehydrodidemnin B or aplidin, an oxidation product of Didemnin B, isolated from Mediterranean tunicate *Aplidium albicans* with apparently more potent anticancer potential is also being developed for its phase I clinical trials in Europe (Sakai et al., 1996).

Similarly, girolline and jaspamide, isolated from the sponge *Pseudoaxyssa cantharella* (Ahond et al., 1988), and the Indo-Pacific sponge *Jaspis splendus* (Crews et al., 1986), respectively, were also withdrawn from the clinical trials due to their extremely toxic side effects. Girolline resulted in hypertension problems in the patients while jaspamide was withdrawn benevolently from the preclinical evaluation stage as it was excessively toxic (Faulkner, 2000). Yondelis® (Reuters.com, 8 May, 2008), a promising anticancer compound, is currently in phase II and phase III clinical trials and has been approved as an Orphan Drug (Haefner, 2003). Conversely, significant hepato- and hemato-toxicities of Yondelis in rats, mice, and monkeys could in fact limit its potential use in the human cancer treatment (Donald et al., 2003).

However, recent study showed that high dose of dexamethasone offered complete protection against the hepatotoxicity in rats by yondelis. Another anticancer compound, LU103793, a dolastatin 15 analogue, has failed to show activity in patients with melanoma and breast cancer in phase II trials, however, trials are continuing in ovarian, prostate, and colon cancer patients (Kerbrat et al., 2003). Besides their therapeutic efficacy studies in tumor xenograft models, these compounds along with many others have not been evaluated for their anticancer potentials in the chemical/oncogene-induced animal carcinogenesis models.

CONCLUSIONS

While discussing drugs of marine origin, it is important to distinguish between molecules providing "drug leads" and those molecules more adequately described as "drug candidates" that are presented here. Despite of the fact that several pharmacologically active marine compounds have been dropped from further drug developments, on account of severe toxicities, still there is a vast scope of finding new drug leads from this colossal source. Marine plants and animals have provided literally hundreds of compounds that can be defined as the former, but few have advanced to the stages of clinical trials. The molecules presented here are thus concrete examples of the exciting advances being made in marine drug discovery. The process discovery and identification of these compounds suggests that they have already contributed significantly to biomedical research and at least some of them may indeed reach the status of clinical trials. Marine drug discovery can prove to be an immensely

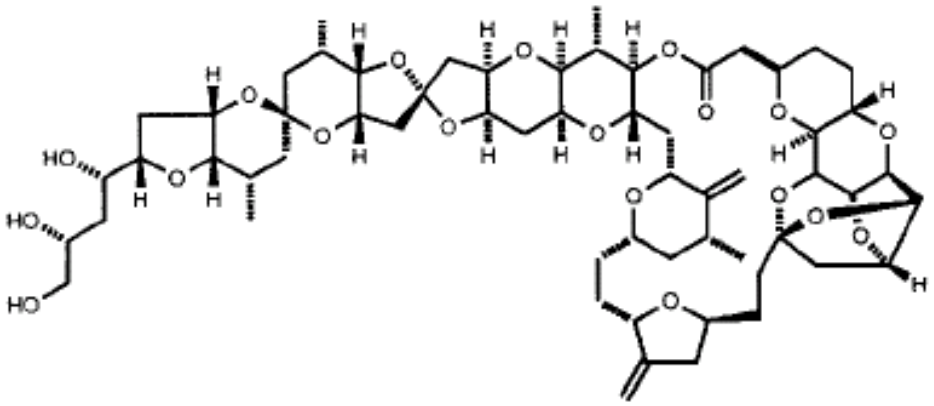

Figure 1. Halichondrin B.

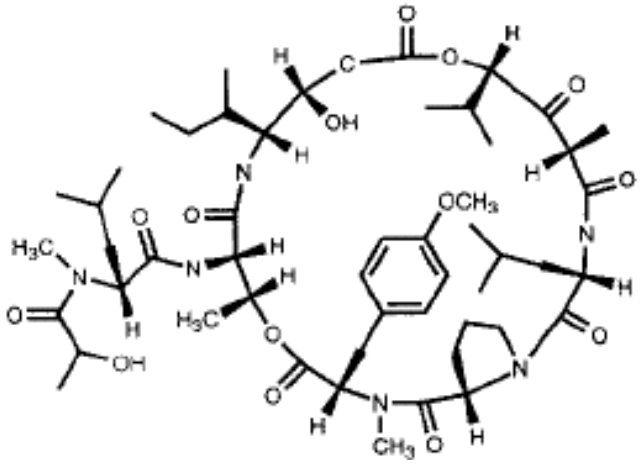

Figure 2. Didemnin B.

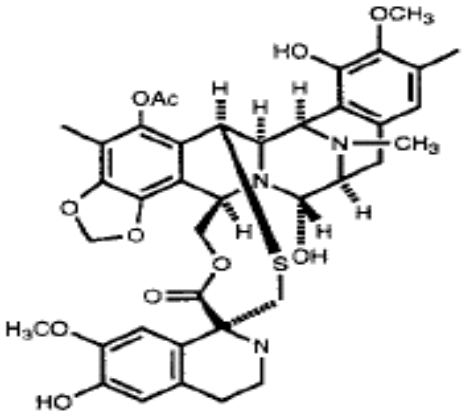

Figure 4. Ecteinascidin 743.

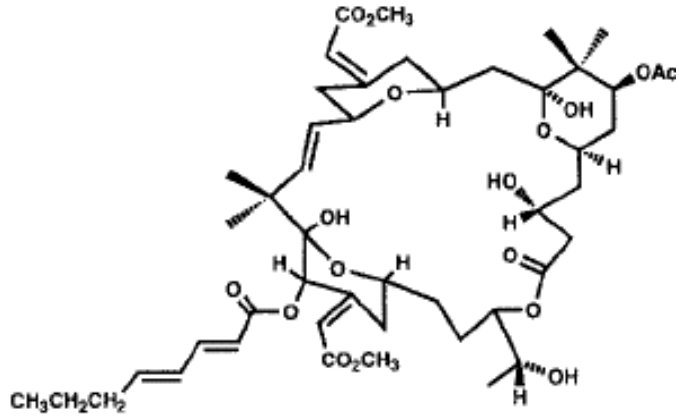

Figure 3. Bryostatin 1.

useful ray of hope for the most dreaded diseases, including cancer. The discovery and invention of a new class of anti cancer agents, known as the vascular disrupting agents, such as the Combretastatins and Sorafenib, also give a ray of hope to cancer patients (Kartikay, 2008). With the marine drug research, making speedy advances, we can expect similar agents from the ocean anytime now. Moreover, the search for better anticancer agents must go on at a war footing even in the lesser investigated marine environments, like the Indian Ocean, where huge unexplored opportunities still lie unearthed (Kartikay, 2009). A thoroughgoing war against cancer, at all fronts is the only viable option left with us.

What appears likely is that studies of new drug leads from marine sources will significantly expand. As the scientific bridges between marine science and drug discovery continue to be built, new collaborations will lead to long-drawn-out pharmacological research. There is no doubt that these global studies will identify novel marine drug candidates in diverse areas of therapeutic development. When one considers the extent of oceanic biodiversity, including such major, uninvestigated groups as marine bacteria and fungi, it seems likely that marine sources could be the major source of new drugs for the succeeding years (Figures 1 to 8).

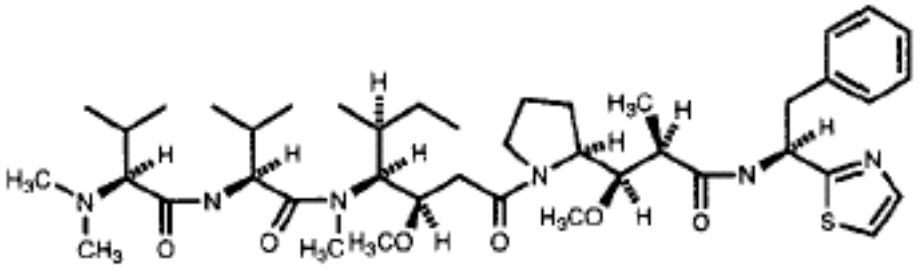

Figure 5. Dolastatin 10.

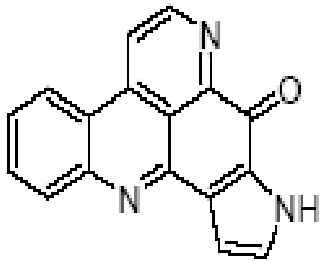

Figure 6. Sebastianine A.

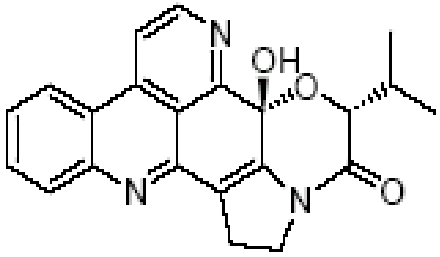

Figure 7. Sebastianine B.

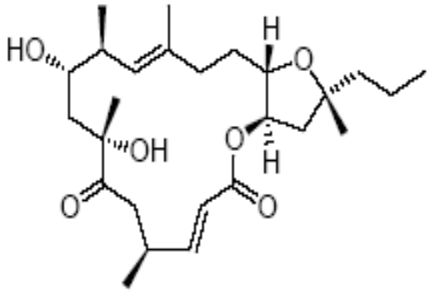

Figure 8. Amphidinolide X. (Some potent anticancer compounds from the ocean).

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