Bioactive substances with anti-neoplastic efficacy from marine invertebrates: *Bryozoa, Mollusca, Echinodermata* and *Urochordata*

Peter Sima, Vaclav Vetvicka

**Abstract**

The marine environment provides a rich source of natural products with potential therapeutic application. This has resulted in an increased rate of pharmaceutical agents being discovered in marine animals, particularly invertebrates. Our objective is to summarize the most promising compounds which have the best potential and may lead to use in clinical practice, show their biological activities and highlight the compounds currently being tested in clinical trials. In this paper, we focused on *Bryozoa, Mollusca, Echinodermata* and *Urochordata*.

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**Key words:** Cancer; *Echinodermata*; Invertebrates; *Mollusca*; *Urochordata*

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**INTRODUCTION**

Oceans contain the greatest known diversity of life, with 34 of the 36 phyla represented. It is not surprising that due to this diversity, a substantial number of biomedically potent molecules have been described, isolated and characterized. At the same time, despite decades of intensive research, cancer is still one of the most lethal diseases. Despite great achievements and decades of intensive, labor-consuming and expensive research, the incidence of various tumors and cancers is still increasing at an alarming rate. Based on the National Cancer Institute estimates, slightly less than one-in-two men and little more than one-in-three women in the United States are likely to contract cancer in their lifetime. In addition, the discovery of new anti-cancer drugs is painfully slow. In fact, very few fundamentally new anti-cancer drugs were introduced in the last decade, thus leaving oncologists to rely on chemotherapeutic drugs developed in the fifties.

In the past 30 years, the role of natural products in drug discovery has undergone many changes. It is not surprising, therefore, that in the past few decades, marine animals (and plants) have been the focus of an intensive effort to identify new molecules with anti-cancer properties. Marine invertebrates contain metabolites of unprecedented molecular structures and activities. In addition, *de novo* synthesis and design of pharmacologically active substances can not replace millions of years of evolution. Despite the fact that only a very small number of marine animals have been investigated, more than 12 000 novel bioactive molecules have been discovered. Several
marine natural products are currently undergoing clinical trials and their success is encouraging. In this part of our review, we focus on the pharmacologically-effective molecules with potential anti-cancer abilities found in Bryozoa, Mollusca, Echinodermata and Urochordata.

**Bryozoa**

Over 4000 living species of Bryozoa are known. Macroyclic lactone bryostatin-1, a very promising anti-tumor metabolite with significant biological activities, was isolated from the bryozoan Bugula neritina\[^1\]. It is a potent immunomodulator promoting hemato-, lympho-, and myelopoiesis, activates protein kinase C, and acts as an antagonist of tumor-promoting phorbol esters\[^2,3\]. Moreover, it down regulates multi drug resistance gene 1 expression, influences bcl-2 and p53 gene expression, and induces apoptotic processes\[^4,5\]. It also has strong anti-cancer activity and simultaneously enhances the activity of chemotherapeutics such as cisplatin, gemcitabine, paclitaxel, and vincristine\[^6,7\]. Bryostatins are already in clinical use\[^8-10\]. Lopanik et al\[^11\] subsequently discovered that bryostatins are actually produced by a microbial symbiont (Endobugula sertula) which protects Bugula larvae from predators using these substances.

The alkaloids, pterocellins, were isolated from another bryozoan, Pterocella vesiculosa\[^12\]. They possess cytotoxic activities against murine leukemia, human melanoma and breast cancer cell lines.

**Mollusca**

The mollusks belong to the most successful evolutionary assemblage of animals. Malacologists estimate that there are up to 150 000 molluscan species living world-wide\[^13\]. Contrary to the vast number of molluscan species and their relative accessibility, not many of their secondary bioactive metabolites have been investigated. Substances exerting anti-cancer activity are mainly peptides, dolastatins, which were first isolated in 1985 from prosobranch mollusk Jorunna funebris. These metabolites could also be accumulated from some sponges (e.g., Enoplaxella sp., Haliclona sp., Oceanapia sp., and Xestospongia sp.), which represent the main source of Jorunna nutrition. They are highly active against human colon, prostate and lung carcinoma cell lines\[^14\].

The other peptide metabolite with anti-tumor activity is the dissipeptide, kahalalide F, which was isolated from the mollusk Ellysia rubescens. It induces cytotoxicity by blocking the G1 phase of cell cycle and has selectivity against cell lines derived from solid tumors like prostate, breast, and colon cancer\[^21\]. Various bioactive peptides, e.g., angiotensin-converting enzyme inhibitory peptides, anti-fungal and anti-cancer peptides\[^22\] were also discovered in oysters. Wang et al\[^23\] treated tumor-bearing mice with oyster peptides and documented a significant inhibition of tumor growth accompanied by an increase in NK cell activity.

An important and very hopeful group of anti-cancer drug candidates are the hexacyclic pyrrole alkaloids, the lamellarsins, which were first isolated in 1985 from prosobranch mollusks of the genus Lamellaria\[^24\]. Over 38 lamellarsins denominated A-Z and a-γ were discovered. It was shown that these substances are effective inhibitors of a number of so-called disease-relevant protein kinases such as cyclin-dependent protein kinases, glycogen synthase kinase 3, serine/threonine kinase Pim-1, and specificity to both the tyrosine phosphorylation regulated kinase 1A, and casein kinase 1, which are involved in cancer cell proliferation. Baunbæk et al\[^25\] showed that 22 lamellarsins inhibit 6 kinases which are essential for transition from G1 to G2 phase and induce cell cycle arrest and cell death. Investigations into the therapeutic effects of these substances and their artificial analogues is ongoing and promises to acquire new, less toxic, but still effective compounds.

**Echinodermata**

Deuterostomian invertebrates-the echinoderms—comprise about 6000 species. The main secondary bioactive metabolites are the saponins. Sulfated glycosides belonging chemically to asterosaponins are regularosides and novaeguinosides from the starfish Culea novaeguineae. These structurally and functionally characterized. Linear monoterpenes and steroids with significant anti-neoplastic activities were also described in the sea hare Notarchus leachi cirrus. Many of these compounds exert promising anti-tumor activity, but they are only available in miniscule amounts\[^26\]. Another macrolide substance-latrunculin A—was first discovered in the sponge Negombata magnifl\[^21\]. It disrupts actin polymerization and binds to actin microfilaments, thereby impairing cellular migration and adhesion. It also suppresses tumor metastases and cellular viability (for review\[^27\]). Other potentially cytotoxic terpenoid derivatives have been discovered—Hexabranthus sanguineus and Pflilidiella pustulosa\[^28\]. Further cytotoxic substances, the bistetrahydroisoquinolines, jorunnamycins A-C, were isolated from the nudibranch gastropod mollusk Jorunna funebris. These metabolites could also be accumulated from some sponges (e.g., Enoplaxella sp., Haliclona sp., Oceanapia sp., and Xestospongia sp.), which represent the main source of Jorunna nutrition. They are highly active against human colon, prostate and lung carcinoma cell lines\[^24\].

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of breast, colon, ovarian, neural and lung origin. The alkaloids, just as in some mollusks, corals and sponges, represent the main group of urochordate metabolites with cytotoxic and antineoplastic activity. The tetracyclic alkaloids, cystaltykins, from tunicate *Cystodytes delichaejia* were the first pyridoacridine alkaloids, interesting levorotatory compounds, discovered in tunicates. These compounds showed potent cytotoxicity against murine lymphoma cells and human epidermoid carcinoma cells in vitro.

Additionally, important tunicate molecules with anti-neoplastic activity against many mammalian tumor cell lines are the polyaromatic alkaloids belonging to the family of lamellarins described previously in the prosobranch mollusk *Lamellaria sp.* (see above), which were isolated from several species of the tunicate genus *Didemnum*. A family of cyclic dispeptide derivatives called didemnins with potent antineoplastic properties was isolated from *Didemnum solidum*, from which didemnin B exerted the highest degree of antitumor activity and was included in clinical trials as early as 1988. Because of its toxic side-effects, it was discarded from further clinical examinations. A similar molecule to didemnin, the aplidine (dehydrodermin B), was extracted from the tunicate *Aplidium albicans*. Aplidine interfered, similar to kahalalide and ecteinascidins, with the cell cycle, however, its cytotoxicity against tumors is based on inhibition of the enzyme ornithine decarboxylase which is required for tumor growth. It also exerts inhibiting activity on HIF-1. Clinical phase II studies confirmed its cytostatic activity against acute lymphoid and myeloid leukemia.

From the point of view of anticancer activity, lipophilic cyclic peptides like ascidiacyclamide, ulithiacyclamide, several patellamides from *Lissoclinum patella* and some polyunsaturated amino alcohols such as crucigerolins from *Pseudodiastoma cruciger* are interesting with regard to therapeutic development. Equally the polyketal, palmerolide A, from the tunicate *Synoicum adareanum*, which was found to be particularly active against melanoma cells, is an attractive substance for the construction of new synthetic derivatives.

The bi-steroidal substance, cephalostatin 1, which activates the apoptosis signals, was recently discovered in a representative of a unique phylum of marine deuterostomian invertebrates, the hemichordate *Cephalodiscus gilchristi*. It inactivates the antiapoptotic mitochondrial protein bel-2 and activates caspase-4, an endoplasmic reticulum stress response and induces apoptosis. These effects strongly suggest that cephalostatin 1 may be useful in the development of a drug to treat drug-resistant cancers.

**CONCLUSION**

The most important bioactive substances with anti-neoplastic effects isolated from these phyla are summarized in Table 1. In general, these substances manifest one or more anti-cancer mechanisms, including induction of apoptosis, enhancement of the effects of chemotherape-
utic drugs, direct cytotoxicity, inhibition of proliferation, impaired cell migration, suppression of metastases, gene regulation, or anti-angiogenesis. Despite the extensive effort and enormous amounts of money used in the development of new types of drugs, significant progress in cancer treatment remains elusive. The use of plants as a source of new drugs resulted in few clinically important drugs, but in recent years, more attention has been focused on marine organisms. Readers seeking additional data should read these excellent articles.[41,51-55] From the data in both sections of this work, it is clear that the world’s oceans will play an important role in the future control of cancer treatment. Although some of the molecules isolated from marine invertebrates are already used for cancer treatment in the United States and the European Union, substantial efforts are still necessary to further advance clinical applications and to fulfill the potential offered by marine invertebrates.

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