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EDITORIAL

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

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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.*

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 biomedicinally 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 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 suprising, 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. Macrocyctic 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, dolabellanins and dolastatins, which are obtained from the albumen glands of the sea hare *Dolabella auricularia*[14-17]. The linear peptides, dolastatin 10 and depsipeptide dolastatin 15, have a strong cytotoxic impact on tumors through the inhibition of cell proliferation. They damage the microtubule cytoskeleton and induce apoptosis in neoplastic cells[18]. Some dolastatins have been selected for further clinical testing.

The cytotoxic substance aplyronine A, a structurally inseparable mixture of four diastereomers of two amino acid esters, and their congeners, aplyronines B-H, were isolated from another species of sea hare, *Aplysia kurodai*[19]. Recently, the bioactive properties of 33 cytotoxic substances including aplyronines and the alkaloids aplaminones isolated from *A. kurodai*, and dolastatin H, isodolastatin H, cyclodepsipeptides aurilide and doliculide, polyketides aurisides A and B, polypropionates auripyrones A and B, macrolides dolabelides A, C and D, and terpenoids auriol and auriculol from D. *Auricularia* were structurally and functionally characterized. Linear monoterpenes and steroids with significant anti-neoplastic activities were also described in the sea hare *Notarchus leachii cirrosus*. Many of these compounds exert promising anti-tumor activity, but they are only available in miniscule amounts[20]. Another macrolide substance-latrunculin A-was first discovered in the sponge *Negombata magnifca*[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[22]). Other potentially cytostatic terpenoid derivatives have been discovered-*Hexabranchus sanguineus* and *Phyllidiella pustulosa*[23]. 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., *Euplacella 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].

The other peptide metabolite with anti-tumor activity is the dissipeptide, kahalalide F, which was isolated from the mollusk *Elysia rubefescens*. 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[25]. Various bioactive peptides, e.g., angiotensin-converting enzyme inhibitory peptides, anti-fungal and anti-cancer peptides[26] were also discovered in oysters. Wang *et al*[27] 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 lamellarins, which were first isolated in 1985 from prosobranch mollusks of the genus *Lamellaria*[28]. Over 38 lamellarins denominated A-Z and α-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*[29] shown that 22 lamellarins 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 asterosaponons are regularosides and novaeguinosides from the starfish *Culcita novaeguineae*. These

Table 1 The most important bioactive substances with anti-neoplastic effects isolated from *Bryozoa*, *Mollusca*, and *deuterostomian* invertebrates

Component	Species	Ref.
Bryostatin-1	*Bugula neritina* (bryozoan)	[1]
Pterocellins	*Pterocella vesiculosa* (bryozoan)	[12]
Dolabellanins	*Dolabella auricularia* (mollusc)	[14]
Dolastatins	*Dolabella auricularia* (mollusc)	[17]
Aplyronine A	*Aplysia kurodai* (mollusc)	[19]
Jorunnamycins A-C	*Jorunna funebris* (mollusc)	[24]
Kahalalide F	*Elysia rubefescens* (mollusc)	[25]
Lamellarins	*Lamellaria sp./Didemnum sp.* (mollusc/tunicate)	[28,39]
Intercedensides	*Mensamaria intercedents* (echinoderm)	[23]
Philinopgeneins	*Pentacta quadrangularis* (echinoderm)	[23]
Colochirosid	*Colochirous anceps* (echinoderm)	[23]
Ritterazine A	*Ritterella tokioka* (tunicate)	[33]
Ecteinascidins	*Ecteinascidia turbinate* (tunicate)	[34]
Cystodytins	*Cystodytes dellechiajei* (tunicate)	[38]
Didemnins	*Tridemnum solidum* (tunicate)	[41]
Ascidiacyclamide	*Lissoclinum patella* (tunicate)	[44]
Cephalostatin 1	*Cephalodiscus gilchristi* (hemichordate)	[50]

exert only marginal cytotoxicty. On the other hand, triterpene glycosides, the intercedensides from sea cucumber *Mensamaria intercedents,* the triterpenoids, philinopgeneins and their analogues philinopsides from *Pentacta quadrangularis*, and the pentalycosid analogue, colochirosid, from *Colochirous anceps* have strong cytotoxicity against human tumor cancer cells. Same of them also exert potent anti-angiogenic activity and therefore could represent promising new drugs[23].

UROCHORDATA

There are approximately 4000 species of urochordates, commonly known as the tunicates. Molecules with cytotoxic and cancerostatic properties were found in these deuterostomian animals[30-32]. A cytotoxic steroidal alkaloid, ritterazine A, was isolated from the tunicate *Ritterella tokioka*[33]. A group of pharmacologically active metabolites with a strong antitumor effect, the tetrahydroisoquinolone alkaloids ecteinascidins from *Ecteinascidia turbinata* were identified[34]. These substances have been under evaluation by the National Cancer Institute for 15 years[35]. In particular, ecteinascidin 743 exhibits numerous bioactive effects in comparison to other ecteinascidins. Similar to the above mentioned kahalalide F, it interferes with cell cycle blocking G2 phase inducing apoptosis, and interacts with the cytoskeletal microtubules as with spongian, coelenterate, and molluscan derivatives[36] (see above). Ecteinascidin 743 has strong antineoplastic potential and has been in preclinical and clinical trials since 2000[37]. It was shown to have activity against melanoma cell lines, and carcinomas of breast, colon, ovarian, neural and lung origin[32].

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, cystodytins**,** from tunicate *Cystodytes dellechiajei* were the first pyridoacridine alkaloids, interesting levorotatory compounds, discovered in tunicates[38]. These compounds showed potent cytotoxicity against murine lymphoma cells and human epidermoid carcinoma cells *in vitro*.

Additionally, important tunicate molecules with antineoplastic activity against many mammalian tumor cell lines are the polyaromatic alkaloids belonging to the family of lamellarins described previously in the prosobranch mollusks *Lamellaria sp.* (see above), which were isolated from several species of the tunicate genus *Didemnum*[39,40]. A family of cyclic dispeptide derivatives called didemnins with potent antineoplastic properties was isolated from *Tridemnum solidum*, from which didemnin B exerted the highest degree of antitumor activity[41] and was included in clinical trials as early as 1988[42]. 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*[43]. Aplidine interfered, similar to kahalalid F and ecteinascidins, with the cell cycle, however, its cytotoxicity against tumors is based on inhibition of the enzyme ornithine descarboxylase which is required for tumor growth[36]. 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 patellamids from *Lissoclinum patella*[44,45], and some polyunsaturated amino alcohols such as crucigasterins from *Pseudodistoma crucigaster*[46] are interesting with regard to therapeutic development. Equally the polyketide, palmerolide A, from the tunicate *Synoicum adareanum*, which was found to be particularly active against melanoma cells[47], is an attractive substance for the construction of new synthetic derivatives[48].

The bi-steriodal 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*[49]. It inactivates the antiapoptotic mitochondrial protein bcl-2[49] and activates caspase-4, an endoplasmic reticulum stress response and induces apoptosis[50]. 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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