Bioactive substances with anti-neoplastic efficacy from marine invertebrates: Porifera and Coelenterata

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Abstract

An ever increasing demand for new lead compounds in the pharmaceutical industry has led scientists to search for natural bioactive products. Based on this extensive research, marine invertebrates now represent a rich source of novel substances with significant anti-neoplastic activities. As the current approach of synthesizing new and chemically modifying old drugs seems to have slowed down, a new approach is clearly needed. The objective of this review is to present up-to-date data on these newer compounds. Based on the data summarized in this short review, it is clear that marine invertebrates represent an extremely important source of compounds with potential anti-cancer effects. Considering that we tested only a tiny number of Porifera and Coelenterata, the best is yet to come.

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Key words: Cancer; Coelenterata; Invertebrates; Porifera

INTRODUCTION

Adaptive (inducible) immunity emerged together with the appearance of jaws, and is based on the rearrangement of very variable molecules of the immunoglobulin superfamily (antibodies, T cell receptors, MHC molecules, etc.) which are produced in myriads of variants. While, adaptive immunity is regarded as unique among the defensive strategies of metazoans, all members of the invertebrate phyla utilize a plethora of substances in their natural immunity ranging from peptides to steroids and alkaloids for defense and preservation of their internal integrity.

Oceans comprise 70% of the Earth’s area and the marine ecosystem represents 95% of the biosphere. Thirty-three of thirty-four animal phyla live in the marine environment. The diversity of species is extraordinary and in tropical reef zones reaches 1000 different species per square meter. Environmental pressures, competition for space, nutrition, and self-defense have led to the production of a diverse array of compounds—the secondary metabolites, which these organisms use for intercommunication within their environment. These communication molecules evolved within the scope of symbiotic interrelations sensu, and de Barry studied cooperation and neutralism followed by competition and parasitism. Many of these molecules also represent ancient defense factors.

Bioactive substances formed by marine organisms such as bacteria, algae, protozoans, and invertebrates/...
vertebrates have attracted attention due to their antiviral, antimicrobial, antiprotozoal, antifungal, antihelminthic, and anticancer properties\textsuperscript{[8,9,10]}. A vast number of these substances are produced by phylogenetically diverse organisms that have different and often unprecedented chemical structures and are able to kill eukaryotic cells. These so-called “natural substances”, or synonymously “secondary metabolites,” are small molecules (generally up to 3000 Da) and have been the focus of anti-cancer research for more than 40 years\textsuperscript{[11]}. The main sources of natural metabolites which exert antitumor activity are from invertebrates, particularly marine invertebrates.

Up to the end of the first decennium of this century, more than 15 000 natural compounds have been isolated mainly from sessile animals, sponges, corals, mollusks, and chordates. These substances belong to very different families of chemical compounds. Some of them have very exotic structures and their bioactive and antineoplastic activities take effect on different levels including blocking metabolic/enzymatic reactions, interrupting cell cycle, and direct cell killing. During the past few years, a large numbers of novel compounds have been reported\textsuperscript{[12-14]}. Some of them have undergone preclinical and clinical trials and it is expected that they will be used therapeutically in the very near future.

Difficulties still persist regarding the development and commercial production of pharmacologically bioactive substances. First, the samples of pharmacological interest are obtainable only in minute quantities from the source. Thus, it is necessary to gather significant amounts of such organisms which could threaten the stability of their ecosystems. In certain countries, this is often unlawful\textsuperscript{[15]}. Second, bioactive substances often have very complicated structures and their isolation or synthesis is very expensive\textsuperscript{[16]}. Third, the source of these bioactive compounds are from microorganisms living in symbiosis\textsuperscript{[17,18]}. The determination and isolation of the responsible bacterial producers of such bioactive substances are rather complicated because microbial communities within the ecological environment containing marine sessile animals are very complex. To date, only a few studies have determined the bacterial symbionts of these substances\textsuperscript{[19-22]}. Currently, only about 5% of the symbiotic bacteria present in marine specimens can be cultivated under standardized conditions. Conversely, interest in the development of novel therapeutics from marine symbiotic microbiota continues to grow\textsuperscript{[23]}. It would be pointless to introduce a list of known substances with antineoplastic activities that have been derived from marine invertebrate animals. The aim of this review is only to draw attention to this relatively new branch of pharmacological science which is a rapidly developing new discipline.

**PORIFERA**

Marine sponges are easy to collect and therefore are among the richest sources of bioactive compounds. There are approximately 6000 species of the phylum *Porifera* living in the sea\textsuperscript{[24]}. Sponges are evolutionary and one of the most successful animal groups\textsuperscript{[25]}. Sponges or their associated microorganisms produce a number of secondary metabolites for self-defense\textsuperscript{[26-28]}. More than 5300 chemically different bioactive substances have been discovered in sponges or their symbiotic microorganisms and every year about 200 new compounds are added. Microorganisms comprise up to 40% of the total mass of some sponge species\textsuperscript{[10]}. Many of these substances have pharmaceutical activities against human diseases such as malaria, AIDS, and particularly cancer\textsuperscript{[29]}. They are chemically classified as alkaloids, lipids, steroids, terpenoids or further compounds\textsuperscript{[30,31]}. Cytotoxic substances described, e.g., in *Strongylocentrotus purpuratus* are mainly polyacetylenic lipid derivatives, glycerol ethers, linear alcohols or fatty acids and their esters. Of these compounds, the durissimol-sext strong activity against human gastric tumor cells (NUGC)\textsuperscript{[32]}. A lipid metabolite, plakorsin B from *Plakortis simplex*, is cytotoxic against COLO-250 and KB-16 carcinoma cells, and chondrillin cytotoxic against the human KB-16 cell line. A macrolide, neopololide, which was isolated from *Incertae sedis* species from the family Neopelitidae (Listiida) is cytotoxic to several cancer cell lines\textsuperscript{[33]} IC\textsubscript{50} values of 1.2 nmol/L against the A549 human lung adenocarcinoma cell line, 5.1 nmol/L against the NCI/ADR-RES ovarian sarcoma cell line, and 0.56 nmol/L against the P388 murine leukemia cell line were found. Strong activity was also found in the PANC-1 pancreatic cancer cell line and the DLD-1 colorectal adenocarcinoma cell line, both of which have p53 mutations. This substance has already been synthesized\textsuperscript{[16]}

Our research is also aimed at the clinical use of secondary metabolites for the therapy of cancer. The secondary metabolites of sponges such as crambescidin-816 (*Crambe crambae*), have been shown to beactive against HCT-16 human colon carcinoma cells (IC\textsubscript{50} = 0.24 g/mL). The additional metabolites, discodermolide (*Discodoruma dissoluta*), halichondrin and isohomohalichondrins (*Halichondria okadai*, *Lissodendoryx* sp.); laulimalide and isolaulimalide (*Cavatensis mugilii*), mycaperoxideB (*Mycale sp.*); and spongistatin (*Hytimo erecta*) should also be mentioned. Numerous drugs from marine sponges have been identified as a source of targeting microtubules\textsuperscript{[35,36]}. The anti-cancer activity of these agents may lie mainly in their inhibitory effects on spindle microtubule dynamics, rather than in their effects on microtubule polymer mass\textsuperscript{[37]}. Substances such asjaspolide, dolastatin, halichondrin, morgenstin, hemiasterlin, dictyostatin, discodermolide, laulimalide, peloruseidel A, and zampanolide influence function and are disruptors of the cytoskeleton similar to taxanes (major classes of tubulin polymerization promoters)\textsuperscript{[37,38]} and some tunicate and molluscan molecules\textsuperscript{[39]}. Pharmacologically interesting substances from sponges are lamellarins\textsuperscript{[40]}, which were first described in mollusks (see below). Recently, anticancer drug research has focused on a group of low molecular inhibitors of hy-
poxic signaling in tumor tissues. These substances target a key regulator of oxygen homeostasis, hypoxia-inducible transcription factor 1 (HIF-1\(^{40}\)), which represents a negative factor in cancer prognosis. In addition, they induce apoptotic cell death through multi-target mechanisms, including inhibition of topoisomerase II interaction with DNA and direct effects on mitochondria. Inhibition of its function not only suppresses tumor growth, but simultaneously enhances chemo- and radiotherapy. As of 1998, only two substances were known to inhibit HIF-1. Since that time, about 15,000 extracts of plants and marine animals have been investigated for the inhibition of HIF-1. Several groups of chemically related substances were discovered in plants and microorganisms and in marine algae, sponges, echinoderms and tunicates. These were mainly sodwanone (activity against T47D breast tumor cells (IC\(_{50} = 15 \mu M/L\)), PC-3 prostate tumor cells (IC\(_{50} = 15 \mu M/L\)) and MDA-MB-231 breast tumor cells (IC\(_{50} = 23 \mu M/L\)), and yardenone-type triterpenoids, furanolidip, homoscalaranes, esterterpenes, norsterterpenes, diacnoxamines, and lamellarin-like substances. They were discovered in lipophilic extracts of the sponges *Axinella sp.*, *Lendenfeldia sp.*, *Diacarnus levii*, and *Dendrilla nigra*. Further HIV-1 inhibiting substances, meroditerpenoids strongylolipid, homoscalaranes, esterterpenes, terpenes and nortriterpenenes, were obtained from the sponge *Petraia* (Strongylophora) *strongylolide*\(^{41}\).

Many of the bioactive substances from sponges are terpenes which have cytotoxicity against L-1210 cells (IC\(_{50}\) between 2.8 and 8.1 g/mL) and KB cells (IC\(_{50}\) between 1.2 and 7.6 g/mL)\(^{42}\). These compounds are biosynthesized from the five carbon isoprene building units and their structural modification leads to the formation of numerous derivatives with various biological properties. Steroidal terpenoids were the first marine isoprenes discovered during the 1930s-1940s\(^{43}\). Today, marine terpenoids encompass an enormous number of derivatives. Monomeric congeners of jaspolides can be classified into terpenes, esterterpenes, terpenes and norsterterpenes. Jaspolide B showed efficacy comparable to that of paclitaxel and seems to be a promising anticancer agent for the treatment of leukemia due to its ability to block the cell cycle during transition from the G2 phase to mitosis and trigger apoptosis. Examples of bicyclic esterterpenes are thorectandrols isolated from sponges (Thorectandra *sp.*), together with the parent compounds palaurolide and palaurol. All these substances inhibited the growth of MALME-3M (melanoma) and MCF-7 (breast) cancer cell lines in the range 30-40 mg/mL. Similarly, petrosa-spongolides, the first chelantane esterterpenic lactones isolated from a new sponge species *Petrosaspongia nigra*, exerted cytotoxicity against the human bronchopulmonary carcinoma cell line. The group of isomalabaricane-type triterpenoids represents stillettelins. Stellettel A was recognized in 1981 as a yellow triterpenoidal pigment from the sponge *Jasipis stellifer*\(^{41}\), and showed significant cytotoxicity against murine leukemia cells. Geoditins, stelliferin-related isomalabaricane triterpenoids, were obtained from the sponges *Geodia aponica* and *Rhabdastrella aff. Disticha*\(^{44,45}\). These substances showed significant cytotoxicity against several human promyelocytic leukemia, prostate, gastric, breast, cervical and hepatocellular carcinoma cell lines such as NSCLC-N6 bronchopulmonary cells (IC\(_{50}\) between 1.0-32.2 mol/L) leukemia P388 cell line (IC\(_{50}\) = 2.1 nmol/L), leukemia cells HL-60 (IC\(_{50}\) = 0.9 mol/L), prostate cancer cells LNCaP (IC\(_{50}\) = 260 mol/L), and stomach cancer cells AGS (IC\(_{50}\) = 2.9 mol/L). Readers seeking more details regarding the 60 cancer cell lines tested should read this comprehensive review\(^{46}\).

Other chemically different groups of diterpenoid substances constitute terpenyl purines. Some of these (agelasines, asmarines) were isolated mainly from the sponge *Agelas sp.* and *Raspailia sp.*. They display a high general toxicity against protozoa and bacteria including cytotoxicity against several cancer cell lines\(^{47}\). This study found cytotoxic effects against lymphoma L1210 cells (IC\(_{50}\) = 3.1 g/mL), and MEL-28 melanoma cells (IC\(_{50}\) = 1.18 mol/L). Another group of spongian substances with antitumor activity are the alkaloids which include pyridoacridine, indole, pyrrole, pyridine, isoquinoline, guanidine and steroidal alkaloids\(^{48}\).

Pyridoacridines are probably the largest class of the marine alkaloids. Pyridoacridines can be divided into tetracyclic, pentacyclic, hexacyclic, heptacyclic and octacyclic alkaloids. Almost all were isolated from sponges, coelenterates, and ascidians. They show significant cytotoxicity against different types of tumors and contain additional specific biological properties. The most pronounced effects are inhibition of topoisomerase II catalytic activity in human colon cancer cells HCT-116. Numerous additional compounds in this group were isolated; most of which are polycyclic (shermilamine, kuanoniamine, neoamphimedine, arnoamines and styelsamines).

Bisindole alkaloids, drabricadin and dragmacidons, were extracted from the sponges *Dragmacidin sp.*, *Spongiosorites sp.*, and *Hexadella sp.*. Several substances in this family were found to be cytotoxic against several human cancer cell lines such as P388 (IC\(_{50}\) = 15 g/mL), lung cells A-549, colon cells HCT-8 and the breast cancer cell line MDA-MB (IC\(_{50}\) = 10 g/mL)\(^{49}\). New bisindole alkaloids, norterpentin, were isolated from the sponge *Spongiosorites rutzelei*. Some exhibited cytotoxic activity against cancer cell lines. Similarly, terpentin and their derivatives from the sponge *Topsentia genitrix* inhibited proliferation of cultured human and murine tumor cells at micromolar concentrations (IC\(_{50}\) values ranged from 4 to 40 mmol/L) and were active against in vitro P388 leukemia (%T/C = 137, 150 mg/kg, QD1-5) and B16 melanoma (%T/C = 144, 37.5 mg/kg, QD1-9) tumors\(^{49}\). Other bisindole alkaloids, hyrtinadine, hyrtosins from the sponge *Hyrtios sp.*, exhibited in vitro cytotoxicity against murine leukemia and human epidermoid carcinoma cells. In addition, β-carboline alkaloids, hyrtiocretines, and hyrtiocarboline from *Hyrtios reticulatus* showed cytotoxicity against murine leukemia L1210 cells (IC\(_{50}\) = 1 µg/mL) and human epidermoid carcinoma KB cells (IC\(_{50}\) = 3 µg/mL) in vitro\(^{50}\). Manzamines and their congeners from the sponge *Ams-
Table 1 The most important bioactive substances with anti-neoplastic effects isolated from Porifera

| Component          | Species                        | Ref.  |
|--------------------|--------------------------------|-------|
| Durissimols        | Stronglyphora durissima        | [50]  |
| Plakorin B         | Plakortis simplex              | [52]  |
| Chondrinil         | Xestospongia sp.               | [52]  |
| Neopeltoidide      | Neopeltidae                    | [52]  |
| Jaspolide          |                                 | [50,4]|
| Dolastatin         |                                 | [50,4]|
| Halichondrin       |                                 | [50,4]|
| Spongistatin       |                                 | [50,4]|
| Dictyostatin       |                                 | [50,4]|
| Discodermolide     |                                 | [50,4]|
| Lauilmalide        |                                 | [50,4]|
| Peloride A         |                                 | [50,4]|
| Zampanolide        |                                 | [50,4]|
| Lamellarins        |                                 | [5]   |
| Sodwanone          | Axinella sp.                   | [52]  |
| Tritterpenoids     | Axinella sp.                   | [52]  |
| Furanolidip        | Axinella sp.                   | [52]  |
| Homosalarane       | Axinella sp.                   | [52]  |
| Sesterterpenes     | Axinella sp.                   | [52]  |
| Norsesterpenes     | Axinella sp.                   | [52]  |
| Diacarosides       | Axinella sp.                   | [52]  |
| Stronglyporines    | Petroxia strongylata           | [52]  |
| Stelletin A        | Jaspis stellifera              | [52]  |
| Agelasines         | Agela sp.                      | [52]  |
| Amaranines         | Agela sp.                      | [52]  |
| Hyrtiacidin        | Dragmacdin sp.                 | [52]  |
| Nortopsentin       | Spongeosorites ruetsleri       | [52]  |
| Topsentin          | Topshenia genzirix             | [52]  |
| Hyrtinidine        | Hyrtin sp.                     | [52]  |
| Hyrtosine          | Hyrtin sp.                     | [52]  |
| Hyrticarboline     | Hyrtin reticulatus             | [52]  |
| Cylindradines      | Axinella cylindratus            | [52]  |
| Agelastatins       | Agelas dendromorpha            | [52]  |
| Ibromophekellstatin| Phakellia mauritiana           | [52]  |

Phimeden sp. also appear to have some potential cancerogenicity towards human hepatocellular carcinoma cells HEPG-2.[53]

Other bioactive substances found in marine sponges are the (brom) pyrrole alkaloids. Cylindradines from Axinella cylindratar displayed moderate cytotoxicity against murine leukemia cells P388[52], and agelastatins (Agelas dendromorpha) and clathrinid (A. clathrodes) showed significant potent in vitro activity against several tumor cell lines. Agelastatin A inhibited OPN protein expression and enhanced expression of the cellular OPN inhibitor, Tcf-4. Agelastatin A treatment also reduced β-catenin protein expression and reduced anchorage-independent growth, adhesion, and invasion in R37 OPN pBK-CMV and C9 cell lines. Similar effects were observed in MDA-MB-231 and MDA-MB-435s human breast cancer cell lines exposed to (-)-agelastatin A[53]. The tetrcyclic pyrrole-imidazole alkaloid, ibromophekellstatin, from Phakellia mauritiana, showed cytostatic activity against a panel of 36 human cancer cell lines in a cell survival and proliferation assay. The ovarian cancer cell line OVXF 899L proved to be most sensitive (IC50 = 0.60 mol/L), followed by the glioblastoma cell line CNXF 498NL (0.93), the nonsmall lung cancer cell line LXF 529L (0.96 mol/L), and the uterine cancer cell line UXF 1138L (1.21 mol/L). The selectivity profile of rac-dibromophakellstatin may be indicative of a novel mechanism of action.[54]

There are many other alkaloids which exert cytotoxic and potentially anticancerogenic activities, which have been identified in various species of marine sponges. Chemically, they belong to the alkaloid groups: the pyrroloquinoline alkaloids (e.g., zyzyzannones, discorhabdins, batzellines, prianosins, makaluvamines, tsitsikammamine), pyrroloquinoline alkaloids (plakinidines), pyrrole alkaloids (perinidins, variolins, halitulins), pyridine alkaloids (pyrindemins, pyridines, amphimedosides, echinoclathrines), isoquinoline alkaloids (cribrostatins), guanidine alkaloids (ptilomycalins, netamines), aminoimidazole alkaloids (leucosolenamines, naamidines), steroidal alkaloids (plakaminines, ritterazines, cortistatins) and many other alkaloid molecules. Our detailed knowledge of these potentially interesting molecules is still limited.

In conclusion, numerous and very different antitumor substances (Table 1) have been isolated from sponges[51]. Many of them are already in clinical use or undergoing the final stages of clinical trials (e.g., antiviral vidarabine or manzaminA with antimalarial, antitubercular and anti-HIV activities)[53].

COELENTERATA

There are two phyla of coelenterate: Cnidaria, comprising more than 9000 species, and Ctenophora with 50 species[54]. Practically all substances with bioactive activities—mainly steroids, terpenes, and other compounds (e.g., ceramides)—were obtained from sea anemones and corals (Anthozoa). The glycosides, cervicosides and prostanoid-sclaviridenones, from the soft corals Sinularia cervicornis and Clavularia viridis were shown to have antitumor activity against human cancer cell lines[51]. A great number of diterpenoids classified into the dollabelane, xenicane, sclaviridenone, from sea anemones and corals (Anthozoa) showed significant antiproliferation activity on cancer cells in vitro and in vivo. The glycosides, cercicosides and prostanoid-sclaviridenones, from the soft corals Sinularia cervicornis and Clavularia viridis were shown to have antitumor activity against human cancer cell lines[51]. 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be correlated with that shown by any other compounds including the currently used anticancer drugs. The correlation coefficient value was less than 0.5 indicating that these substances may have a new mode of action. Another experiments showed moderate cytotoxic activity against human colorectal adenocarcinoma cells (DLD-1) with an IC₅₀ of 5.0 μg/mL. The lobane diterpenes and lobane lactones (menverins) and several lipidic substances. As an example, strong and increasing polymerization. In addition, this natural product was shown to be a potent cancer cell inhibitor with an IC₅₀ similar to that of paclitaxel (Taxol®) (10-15 nmol/L), and assays in the National Cancer Institute’s 60 cell line panel showed a 100-fold greater potency over the mean cytotoxicity towards breast, renal, ovarian and lung cancer cell lines. Secondary bioactive metabolites were also discovered in gorgonians. They are mainly steroids and terpenoids and several lipidic substances. As an example, strong and selective cytotoxicity was documented for the oxygenated lactones (menverins) from *Menella verrucosa*. Fureen sesquiterpenoids from *Acanthogorgia vegae* exhibited significant cytotoxicity towards the growth of A549, HT-29, KB, P-388 and P-388 cells. For a summary of the most important anticancer molecules (Table 2).

**CONCLUSION**

Drug discoveries from marine invertebrates have enjoyed a renaissance. Currently, interest in evaluating marine invertebrate products, with the aim of obtaining new antitumor drugs with few side effects, is still growing. In many cases (particularly in sponges), the interesting materials (or the whole organisms) are difficult to obtain in sufficient amounts and researchers, therefore, have to start copying nature and preparing synthetic versions. Some of these therapeutics were approved in the United States and the European Union and many are in the final stages of clinical trials. Not surprisingly, the outlook for the future is more promising than ever.

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**Table 2 The most important bioactive substances with anti-neoplastic effects isolated from *coelenterata***

| Component       | Species                              | Ref. |
|-----------------|--------------------------------------|------|
| Cervicosides    | *Sinularia cervicornis*              | [64] |
| Claviridenones  | *Clavularia viridis*                 | [61] |
| Dollabelane     | *Nepheta sp.*                       | [57] |
| Xenicane        | *Nepheta sp.*                       | [57] |
| Phenylgermacrane| *Nepheta sp.*                       | [57] |
| Clavulactones   | *Clavularia sp.*                    | [57] |
| Clavilides      | *Clavularia sp.*                    | [57] |
| Clavudiolis     | *Clavularia sp.*                    | [57] |
| Cembrane        | *Clavularia sp.*                    | [54] |
| Eleutherobin     | *Eleutherobin sp.*                  | [64] |
| Sarcodictyin    | *Sarcodictyon roseum*               | [62] |
| Menverins       | *Menella verrucosa*                 | [63] |
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