World Journal of Clinical Oncology

Online Submissions: http://www.wjgnet.com/2218-4333office
wjco@wjgnet.com
doi:10.5306/wjco.v2.i11.355

World J Clin Oncol 2011 November 10; 2(11): 355-361
ISSN 2218-4333 (online)

EDITORIAL

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

Peter Sima, Vaclav Vetvicka

Peter Sima, Institute of Microbiology, Czech Academy of Sciences, 142 20 Prague 15400, Czech Republic
Vaclav Vetvicka, Department of Pathology, University of Louisville, Louisville, KY 40292, United States
Author contributions: Both authors contributed equally.
Correspondence to: Vaclav Vetvicka, PhD, Professor, Department of Pathology, University of Louisville, 611 S. Floyd Street, Louisville, KY 40292,
United States. vaclav.vetvicka@louisville.edu
Telephone: +1-502-852-1612 Fax: +1-502-852-1177
Received: July 6, 2011 Revised: October 10, 2011
Accepted: October 17, 2011
Published online: November 10, 2011

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, and the identification of new anticancer drugs is not too promising, 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.

Key words: Cancer; Coelenterata; Invertebrates; Porifera

Peer reviewers: Bruna Scaggiante, PhD, Assistant Professor of Molecular Biology and Aggregate Professor of Molecular Biology, Department of Life Sciences, University of Trieste, Via Licio Giorgeri 1, 34127 Trieste, Italy; T H Marczylo, PhD, Endocannabinoid Research Group, Cancer Studies and Molecular Medicine, University of Leicester, Leicester, LE2 7LX, United Kingdom

Sima P, Vetvicka V. Bioactive substances with anti-neoplastic efficacy from marine invertebrates: *Porifera* and *Coelenterata*. *World J Clin Oncol* 2011; 2(11): 355-361 Available from: URL: http://www.wjgnet.com/2218-4333/full/v2/i11/355.htm DOI: http://dx.doi.org/10.5306/wjco.v2.i11.355

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[1,2].

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[3]. The diversity of species is extraordinary and in tropical reef zones reaches 1000 different species per square meter[4,5]. 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[6] studied protocooperation and neutralism followed by competition and parasitism. Many of these molecules also represent ancient defense factors[7,8].

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[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 anticancer research for more than 40 years[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[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[15]. Second, bioactive substances often have very complicated structures and their isolation or synthesis is very expensive[16]. Third, the source of these bioactive compounds are from microorganisms living in symbiosis[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[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[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[24]. Sponges are evolutionary and one of the most successful animal groups[25]. Sponges or their associated microorganisms produce a number of secondary metabolites for self-defense[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[10].

Many of these substances have pharmaceutical activities against human diseases such as malaria, AIDS, and particularly cancer[29]. They are chemically classified as alkaloids, lipids, steroids, terpenoids or further compounds[30,31]. Cytotoxic substances described, e.g., in *Strongylophora durissima* are mainly polyacetylenic lipid derivatives, glycerol ethers, linear alcohols or fatty acids and their esters. Of these compounds, the durissimolsexert strong activity against human gastric tumor cells (NUGC)[32]. A lipid metabolite, plakorsin B from *Plakortis simplex*, is cytotoxic against COLO-250 and KB-16 carcinoma cells, and chondrillinis cytotoxicagainst the human KB-16 cell line. A macrolide, neopeltolide**,** which was isolated from *Incertae sedis* species from the family *Neopeltidae* (*Lithistida*) is cytotoxic to several cancer cell lines[33]. IC_{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[34].

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 crambe*), have been shown to beactive against HCT-16 human colon *carcinoma* cells (IC_{50} = 0.24 g/mL). The additional metabolites, discodermolide (*Discodermia dissoluta*), halichondrins and isohomohalichondrins (*Halichondria okadai, Lissodendoryx sp.*), laulimalide and isolaulimalide (*Cavospongia mycofijinsis*), mycaperoxideB (*Mycala sp.*) and spongistatin (*Hyrtios erecta*) should also be mentioned. Numerous drugs from marine sponges have been identified as a source of targeting microtubules[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[35]. Substances such asjaspolide, dolastatin, halichondrin, spongistatin, hemiasterlin, dictyostatin, discodermolide, laulimalide, pelorusideA, and zampanolide influence function and are disruptors of the cytoskeleton similar to taxanes (major classes of tubulin polymerization promoters)[37,38] and some tunicate and molluscan molecules[13].

Pharmacologically interesting substances from sponges are lamellarins[39], 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 I, 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 μmol/L), PC-3 prostate tumor cells (IC_{50} = 15 μmol/L) and MDA-MB-231 breast tumor cells (IC_{50} = 23 μmol/L), and yardenone-type triterpenoids, furanolipid, homoscalaranesesterterpenes, norsesterterpenesdiacarnoxides, 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 strongylophorines were isolated from the sponge *Petrosia* (*Strongylophora*) *strongylata*[10].

Many of the bioactive substances from sponges are terpeneswhich havecytotoxicity 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)[41]. 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[42]. Today, marine terpenoids encompass an enormous number of derivatives. Monomeric congeners of jaspolides can be classified into triterpenes, sesterterpenes, terpenes and nortriterpenes. JaspolideB 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 sesterterpenes are thorectandrols isolated from sponge (*Thorectandra sp*.) together with the parent compounds palauolide and palauolol. 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, petrosaspongiolides, the first cheilantane sesterterpene lactones isolated from a new sponge species *Petrosaspongia nigra,* exerted cytotoxicity against the human bronchopulmonary carcinoma cell line. The group of isomalabaricane-type triterpenoids representsstelletins. Stelletin A was recognized in 1981 as a yellow triterpenoidal pigment from the sponge *Jaspis stellifera*[43], and showed significant cytotoxicity against murine leukemia cells. Geoditins, stelliferin-related isomalabaricane triterpenoids, were obtained from the sponges *Geodia aponica* and *Rhabdastrella aff. Distinca*[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[43].

Other chemically different groups of diterpenoid substances constitute terpenyl purines. Some of these (agelasines, asmarines) were isolated mainly from the sponge genera *Agela sp*. and *Raspailia sp*. They display a high general toxicity against protozoa and bacteria including cytotoxicity against several cancer cell lines[46]. 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[47].

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, dragmacidin and dragmacidons, were extracted from the sponges *Dragmacidin sp., Spongosorites 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)[48]. New bisindole alkaloids, nortopsentins, were isolated from the sponge *Spongosorites ruetzleri*. Some exhibited cytotoxic activity against cancer cell lines. Similarly, topsentins 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 vivo* 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, hyrtinadineand hyrtosins from the sponge *Hyrtios sp*., exhibited *in vitro* cytotoxicity against murine leukemia and human epidermoid carcinoma cells. In addition, β-carboline alkaloids, hyrtioerectinesand hytriocarboline-from *Hyrtios reticulates* 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 *Am-*

Table 1 The most important bioactive substances with anti-neoplastic effects isolated from *Porifera*

Component	Species	Ref.
Durissimols	*Strongylophora durissima*	[32]
Plakorsin B	*Plakortis simplex*	[32]
Chondrillin	*Xestospongia sp.*	[32]
Neopeltolide	*Neopeltidae*	[33]
Jaspolide		[37,38]
Dolastatin		[37,38]
Halichondrin		[37,38]
Spongistatin		[37,38]
Hemiasterlin		[37,38]
Dictyostatin		[37,38]
Discodermolide		[37,38]
Laulimalide		[37,38]
Peloruside A		[37,38]
Zampanolide		[37,38]
Lamellarins		[39]
Sodwanone	*Axinella sp.,*	[10]
Triterpenoids	*Axinella sp.,*	[10]
Furanolipid	*Axinella sp.,*	[10]
Homoscalarane sesterterpenes	*Axinella sp.,*	[10]
Norsesterterpenes	*Axinella sp.,*	[10]
Diacarnoxides	*Axinella sp.,*	[10]
Strongylophorines	*Petrosia strongylata*	[10]
Stelletin A	*Jaspis stellifera*	[44]
Agelasines	*Agela sp.*	[46]
Asmarines	*Agela sp.*	[46]
Dragmacidin	*Dragmacidin sp.,*	[48]
Nortopsentins	*Spongosorites ruetzleri*	[48]
Topsentins	*Topsentia genitrix*	[49]
Hyrtinadine	*Hyrtios sp.*	[50]
Hyrtosins	*Hyrtios sp.*	[50]
Hyrtioerectines	*Hyrtios reticulates*	[50]
Hytriocarboline	*Hyrtios reticulates*	[50]
Cylindradines	*Axinella cylindratus*	[52]
Agelastatins	*Agelas dendromorpha*	[53]
Dibromophakellstatin	*Phakellia mauritiana*	[54]

phimedon sp. also appear to have some potential cancerogencity towards human hepatocellular carcinoma cells HEPG-2[51].

Other bioactive substances found in marine sponges are the (brom) pyrrole alkaloids. Cylindradines from *Axinella cylindratus* displayed moderate cytotoxicity against murine leukemia cells P388[52], and agelastatins (*Agelas dendromorpha*) and clathrodin (*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 tetracyclic pyrrole-imidazole alkaloid, dibromophakellstatin, 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 (IC_{50} = 0.60 mol/L), followed by the glioblastoma cell line CNXF 498NL (0.93), the non-small 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., zyzzyanones, discorhabdins ,batzellines, prianosins, makaluvamines,tsitsikammamme s), pyrroloacridine alkaloids (plakinidines), pyrrole alkaloids (perinadines, variolins, halitulins), pyridine alkaloids (pyrinodemins, pyrinadines, amphimedosides, echinoclathrines), isoquinoline alkaloids (cribrostatins), guanidine alkaloids (ptilomycalins, netamines), aminoimidazole alkaloids (leucosolenamines, naamidines), steroidal alkaloids (plakinamines, 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[31]. Many of them are already in clinical use or undergoing the final stages of clinical trials (e.g., antiviral vidarabin or manzaminA with antimalaric, antituberculitic and anti HIV activities)[55].

COELENTERATA

There are two phyla of *coelentrates*: *Cnidaria,* comprising more than 9000 species, and *Ctenophora* with 50 species[56]. 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[31]. A great number of diterpenoids classified into the dollabelane, xenicane, phenylgermacrane, and cembranegroups showing cytotoxicity against cancer cell lines were isolated from *Nephe-ta sp*., as did the clavulactones, clavirolides and clavudiols isolated from *Clavularia sp*. For example, these substances were examined for growth-inhibition activities *invitro* toward human cancer cells using the Japanese Foundation for Cancer Research 39 cell line assay. The results showedinhibition of the proliferation of NCI-H522 cells (lung cancer) with an IC_{50} of 0.66 μg/mL, and of LOX-IMVI cells (melanoma) and MKN74 cells (stomach cancer) with an IC_{50} of 0.72 and 0.81 μg/mL, respectively. The pattern of differential growth inhibition was evaluated by the Compare Program and was revealed not to

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

Component	Species	Ref.
Cervicosides	*Sinularia cervicornis*	[31]
Claviridenones	*Clavularia viridis*	[31]
Dollabelane	*Nepheta sp.*	[57]
Xenicane	*Nepheta sp.*	[57]
Phenylgermacrane	*Nepheta sp.*	[57]
Clavulactones	*Clavularia sp.*	[57]
Clavirolides	*Clavularia sp.*	[57]
Clavudiols	*Clavularia sp.*	[57]
Cembrane	*Sinularia sp.*	[59]
Eleutherobin	*Eleutherobia sp.*	[60]
Sarcodictyin	*Sarcodictyon roseum*	[62]
Menverins	*Menella verrucosa*	[65]

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[57]. Another experiments showed moderate cytotoxic activity against human colorectal adenocarcinoma cells (DLD-1) with an IC_{50} of 5.0 μg/mL. The lobane diterpenes and lobane lacatnes, the pacifins from *Sinularia sp.* and *Lobophytum sp.* appear to have similar cytotoxicity. A number of diterpenoids of the xenicane groups from *Xenia sp.* exhibited mild-to-potent cytotoxic activities against human lung carcinoma (H460) and liver carcinoma (HepG2) cell lines[58]. The cembrane substances mainly from *Sinularia* sp. and polyoxygenated steroids from *Alcyonum patagonicum* and another coral species (*Nephtea*) represent the most numerous group of coral diterpenoids which have mild-to-strong cytotoxicity to the human tumor cell lines CCRF-CEM and DLD-1[59]. Other hopeful soft coral cytotoxic and cytostatic substances are eleutherobin[60,61] and sarcodictyin[62,63], which interfere with microtubulins by increasing polymerization. In addition, this natural product was shown to be a potent cancer cell inhibitor with an IC_{50} 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[64].

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)[65] from *Menella verrucosa*. Furean sesquiterpenoids from *Acanthogorgia vegae* exhibited significant cytotoxicity toward the growth of A549, HT-29, KB, P-388 and P-388 cells[66]. 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[67]. Not surprisingly, the outlook for the future is more promising then ever.

REFERENCES

1 **Hughes AL**, Yeager M. Molecular evolution of the vertebrate immune system. *Bioessays* 1997; **19**: 777-786
2 **Zapata A**, Amemiya CT. Phylogeny of lower vertebrates and their immunological structures. *Curr Top Microbiol Immunol* 2000; **248**: 67-107
3 **Rosenthal J**, Investing in biological diversity. Proc Cairns Conf; Cairns:OECD; 1996:1-56
4 **Pomponi SA**, The bioprocess-technological potential of the sea. *J Biotechnol* 1999; **70**: 5-13
5 **Jimeno JM**.A clinical armamentarium of marine-derived anti-cancer compounds. *Anticancer Drugs* 2002; **13** Suppl 1: S15-S19
6 **De Bary AH**. Die Erscheinung der Symbiose. Naturforsch Versamml: Cassel, 1869: 1-103
7 **Williams DH**, Stone MJ, Hauck PR, Rahman SK. Why are secondary metabolites (natural products) biosynthesized? *J Nat Prod* 1989; **52**: 1189-1208
8 **Šima P**, Trebichavsky I, Sigler K. Non-mammalian antibiotic peptides. *Folia Microbiol* 2003; **48**: 709-724
9 **Donia M**, Hamann MT. Marine natural products and their potential applications as anti-infective agents. *Lancet Infect Dis* 2003; **3**: 338-348
10 **Nagle DG**, Zhou Y-D.Marine Natural Products as Inhibitors of Hypoxic Signaling in Tumors. *Phytochem Rev* 2009; **8**: 415-429
11 **Kinghorn AD**, Drug discovery from natural products. In: Lemke TL, Williams DA, editors, Foye's Principles of Medicinal Chemistry. 6th ed. Philadelphia: Wolters Kluwer/Williams and Wilkins, 2008: 12-25
12 **Mayer AM**, Gustafson KR. Marine pharmacology in 2000: antitumor and cytotoxic compounds. *Int J Cancer* 2003; **105**: 291-299
13 **Amador ML**, Jimeno J, Paz-Ares L, Cortes-Funes H, Hidalgo M. Progress in the development and acquisition of anticancer agents from marine sources. *Ann Oncol* 2003; **14**: 1607-1615
14 **Blunt JW**, Copp BR, Hu WP, Munro MH, Northcote PT, Prinsep MR. Marine natural products. *Nat Prod Rep* 2009; **26**: 170-244
15 **Munro MHG**, Blunt JW, Lake RJ, Litaudon M, Battershill CN, Page MJ. From seabed to sickbed: What are the prospects? In: Van Soest RWM, van Kempen TMG, Braekman JC, editors. Sponges in time and space. Rotterdam: A.A. Balkema, 1994: 473-484
16 **Pomponi SA**, Willoughby R. Sponge cell culture for production of bioactive metabolites. In: Van Soest RWM, van Kempen TMG, Braekman JC, editors. Sponges in time and space. Rotterdam: A.A. Balkema, 1994: 395-400
17 **Thoms C**, Schupp PJ. Biotechnological potential of marine sponges and their associated bacteria as producers of new pharmaceuticals (Part I). *J Internat Biotechnol Law* 2005; **2**: 217–220
18 **Thoms C**, Schupp PJ.Biotechnological potential of marine sponges and their associated bacteria as producers of new pharmaceuticals (Part II). *J Internat Biotechnol Law* 2005; **2**: 257–264
19 **Bewley CA**, Faulkner DJ. Lithistid sponges: Star performers

or hosts to the stars? *Angewandte Chemie International Edit* 1998; **37**: 2162–2178
20 **Schmidt EW**, Obraztsova AY, Davidson SK, Faulkner DJ, Haygood MG. Identification of theantifungal peptide-containing symbiont of the marine sponge T. swinhoei as a novel deltaproteobacterium, "Candidatus Entotheonella palauensis". *Mar Biol* 2000; **136**: 969–977
21 **Burja AM**, Hill RT. Microbial symbionts of the Australian Great Barrier Reef sponge, Candidaspongia flabellata. *Hydrobiologia* 2001; **461**: 41–47
22 **Schupp PJ**, Kohlert-Scupp C, Whitefield S, Engemann A, Rohde S, Hemscheldt T, Pezzuto JM. Cancer chemopreventive and anticancer evaluation of extracts and fractions from marine macro- and micro-organisms collected from twilight zone waters around Guam. *Nat Prod Comm* 2009, **4**: 1717-1728
23 **Penesyan A**, Kjelleberg S, Egan S. Development of novel drugs from marine surface associated microorganisms. *Mar Drugs* 2010; **8**: 438-459
24 Berquist PR. Sponges. Berkeley: University of California Press, 1978
25 **Sipkema D**, Franssen MC, Osinga R, Tramper J, Wijffels RH. Marine sponges as pharmacy. *Mar Biotechnol* (NY) 2005; **7**: 142-162
26 **Proksch P**. Defensive roles for secondary metabolites from marine sponges and sponge-feeding nudibranchs.*Toxicon* 1994; **32**: 639-655
27 **Větvička V**, Šima P. Evolutionary mechanism of defense reactions. Berlin: Birkhauser Verlag, 1998: 1-196
28 **Fusetani N**, Kem W. Marine toxins: an overview. *Prog Mol Subcell Biol* 2009; **46**: 1-44
29 **Kikuchi A**, Nieda M, Schmidt C, Koezuka Y, Ishihara S, Ishikawa Y, Tadokoro K, Durrant S, Boyd A, Juji T, Nicol A. In vitro anti-tumour activity of alpha-galactosylceramide-stimulated human invariant Valpha24+NKT cells against melanoma. *Br J Cancer* 2001; **85**: 741-746
30 **Tan G**, Gyllenhaal C, Soejarto DD. Biodiversity as a source of anticancer drugs. *Curr Drug Targets* 2006; **7**: 265-277
31 **Zhang W**, Guo YW, Gu Y. Secondary metabolites from the South China Sea invertebrates: chemistry and biological activity. *Curr Med Chem* 2006; **13**: 2041-2090
32 **Shen YC**, Prakash CV. Two new acetylenic derivatives and a new meroditerpenoid from a Taiwanese marine sponge Strongylophora durissima. *J Nat Prod* 2000; **63**: 1686-1688
33 **Wright AE**, Botelho JC, Guzmán E, Harmody D, Linley P, McCarthy PJ, Pitts TP, Pomponi SA, Reed JK. Neopeltolide, a macrolide from a lithistid sponge of the family Neopeltidae. *J Nat Prod* 2007; **70**: 412-416
34 **Youngsaye W**, Lowe JT, Pohlki F, Ralifo P, Panek JS. Total synthesis and stereochemical reassignment of (+)-neopeltolide. *Angew Chem Int Ed Engl* 2007; **46**: 9211-9214
35 **Zhou J**, Giannakakou P. Targeting microtubules for cancer chemotherapy. *Curr Med Chem Anticancer Agents* 2005; **5**: 65-71
36 **Miller JH**, Singh AJ, Northcote PT. Microtubule-stabilizing drugs from marine sponges: focus on peloruside A and zampanolide. *Mar Drugs* 2010; **8**: 1059-1079
37 **Kingston DG**.Tubulin-interactive natural products as anticancer agents. *J Nat Prod* 2009; **72**: 507-515
38 **Saito SY**.Toxins affecting actin filaments and microtubules. *Prog Mol Subcell Biol* 2009; **46**: 187-219
39 **Urban S**, Hobbs L, Hooper JNA, Capon RJ, Lamellarins Q an R: new aromatic metabolites from Australian marine sponge Dendrilla cactos. *Aust J Chem* 1995; **48**: 1491-1494
40 **Semenza GL**, Wang GL. A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol Cell Biol* 1992; **12**: 5447-5454
41 **Ebada SS**, Lin W, Proksch P. Bioactive sesterterpenes and triterpenes from marine sponges: occurrence and pharmacological significance. *Mar Drugs* 2010; **8**: 313-346
42 **Bergmann W**, Johnson TB. The chemistry of marine animals. I. The sponge Microciona pralifera. *Z Physiol Chem* 1933; **222**: 220–226
43 **Ravi BN**, Wells RJ, Croft KD.Malabaricane triterpenes from a Fijian collection of the sponge Jaspis stellifera. *J Org Chem* 1981; **46**: 1998–2001
44 **Zhang WH**, Che CT. Isomalabaricane-type nortriterpenoids and other constituents of the marine sponge Geodia japonica. *J Nat Prod* 2001; **64**: 1489-1492
45 **Lv F**, Deng Z, Li J, Fu H, van Soest RW, Proksch P, Lin W. Isomalabaricane-type compounds from the marine sponge Rhabdastrella aff. distincta. *J Nat Prod* 2004; **67**: 2033-2036
46 **Gordaliza M**. Terpenyl-purines from the sea.*Mar Drugs* 2009; **7**: 833-849
47 **Kumar D**, Rawat DS. 7. Marine natural alkaloids as anticancer agents. *Opp Challenge Scope Nat Prod Med Chem* 2001; **37**: 213-268
48 **Jiang B**, Smallheer JM, Amaral-Ly C, Wuonola MA. Total synthesis of (±) Dragmacidin: A cytotoxic bis(indole)alkaloid of marine origin. *J Org Chem* 1994; **59**: 6823-6827
49 **Burres NS**, Barber DA, Gunasekera SP, Shen LL, Clement JJ.Antitumor activity and biochemical effects of topsentin. *Biochem Pharmacol* 1991; **42**: 745-751
50 **Endo T**, Tsuda M, Fromont J, Kobayashi J. Hyrtinadine A, a bis-indole alkaloid from a marine sponge. *J Nat Prod* 2007; **70**: 423-424
51 **Samoylenko V**, Khan SI, Jacoba MR, Tekwani BL, Walker LA, Hufford CD, Muhammad I. Bioactive (+)-manzamine A and (+)-8-hydroxymanzamine A tertiary bases and salts from Acanthostrongylophora ingens and their preparations. *Nat Prod Commun* 2009; **4**: 185-192
52 **Kuramoto M**, Miyake N, Ishimaru Y, Ono N, Uno H. Cylindradines A and B: novel bromopyrrole alkaloids from the marine sponge Axinella cylindratus. *Org Lett* 2008; **10**: 5465-5468
53 **Mason C**, McFarlane S, Johynson PG, Crowe P, Erwin PJ, Domostoj MM, Campbell FC, Manaviazar S, Hale KJ, El-Tanadi M. Agelastatin A: a novel inhibitor of osteopontin-mediated adhesion, invasion, and colony formation. *Mol Canc Therapeut* 2008; **7**: 548-558
54 **Zöllinger M**, Kelter G, Fiebig HH, Lindel T. Antitumor activity of the marine natural product dibromophakellstatin in vitro. *Bioorg Med Chem Lett* 2007; **17**: 346-349
55 **Laport MS**, Santos OC, Muricy G. Marine sponges: potential sources of new antimicrobial drugs. *Curr Pharm Biotechnol* 2009; **10**: 86-105
56 **Barnes RD**. Invertebrate Zoology. ., Philadelphia: Saunders College Publishing, 1987
57 Iwashima M, Matsumoto Y, Takenaka Y, Iguchi K, Yamori T. A new marin B, novel diterpenoidic alcohols esterified by (E)-N(1)-methylurocanic acid. Isolation from the Mediterranean stolonifer Sarcodictyon roseum. *Helv Chim Acta* 1987; **70**: 2019–2027
58 **Su JH**, Wen ZH. Bioactive cembrane-based diterpenoids from the soft coral Sinularia triangular. *Mar Drugs* 2011; **9**: 944-951
59 **Duh CY**, Wang SK, Chu MJ, Sheu JH.Cytotoxic sterols from the soft coral Nephthea erecta. *J Nat Prod* 1998; **61**: 1022-1024
60 **Lindel T**, Jensen PR, Fenical W, Long BH, Casazza AM, Carboni J, Fairchild CR. Eleutherobin, a new cytotoxin that mimics paclitaxel (Taxol) by stabilizing microtubules. *J Am Chem Soc* 1997; **119**: 8744–8745
61 **Long BH**, Carboni JM, Wasserman AJ, Cornell LA, Casazza AM, Jensen PR, Lindel T, Fenical W, Fairchild CR. Eleutherobin, a novel cytotoxic agent that induces tubulin polymerization, is similar to paclitaxel (Taxol). *Cancer Res* 1998; **58**: 1111-1115
62 **Burres NS**, Barber DA, Gunasekera SP, Shen LL, Clement JJ.Antitumor activity and biochemical effects of topsentin. *Biochem Pharmacol* 1991; **42**: 745-751

63 **Hamel E**, Sackett DL, Vourloumis D, Nicolaou KC. The coral-derived natural products eleutherobin and sarcodictyins A and B: effects on the assembly of purified tubulin with and without microtubule-associated proteins and binding at the polymer taxoid site. *Biochemistry* 1999; **38**: 5490-5498
64 **McDaid HM**, Bhattacharya SK, Chen XT, He L, Shen HJ, Gutteridge CE, Horwitz SB, Danishefsky SJ. Structure-activity profiles of eleutherobin analogs and their cross-resistance in Taxol-resistant cell lines. *Cancer Chemother Pharmacol* 1999; **44**: 131-137
65 **Li L**, Wang CY, Huang H, Mollo E, Cimino G, Guo YW. Further highly oxygenated guaiane lactones from the South Sea gorgonian Menella sp. *Helv Chim Acta* 2008; **91**: 111-117
66 **Park HW**, Choi SU, Baek NI, Kim SH, Eun JS, Yang JH, Kim DK. Guaiane sesquiterpenoids from Torilis japonica and their cytotoxic effects on human cancer cell lines. *Arch Pharm Res* 2006; **29**: 131-134
67 **Molinski TF**, Dalisay DS, Lievens SL, Saludes JP.Drug development from marine natural products. *Nat Rev Drug Discov* 2009; **8**: 69-85

S- Editor Yang XC **L- Editor** Webster JR **E- Editor** Yang XC