Chapter 1
Introduction to Anticancer Drugs from Marine Origin

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Abstract The chemical and biological diversity of the marine environment is extraordinary resource for the discovery of new anticancer drugs. Recent technological and methodological advances in elucidation of structure, synthesis, and biological assay have resulted in the isolation and clinical evaluation of various novel anticancer agents from marine pipeline. To understanding the marine derived anticancer compounds are useful in pharmaceutical industry and clinical applications. The marine sponges, algae, microbes, tunicates and other species from the marine pipeline are the important sources for biological active compounds. The past decade has seen a dramatic increase in the number of preclinical anticancer lead compounds from diverse marine life enter human clinical trials.

Keywords Anticancer · Algae · Sponges · Marine · Bioactive compounds

1.1 Introduction

Cancer is a dreadful human disease, increasing with changing life style, nutrition, and global warming. A report released by the World Health Organization (WHO) showed that an estimated 12.7 million people were diagnosed with cancer globally and about 7.6 million people died of it in 2008. As estimated in this report, more than 21 million new cancer cases and 13 million deaths are expected by 2030. Although cancer accounts for around 13 % of all deaths in the world, more than 30 % of cancer deaths can be prevented by modifying or avoiding key risk factors [1]. However, almost all of the chemotherapy drugs currently in the market cause serious side effects. Natural products and their derivatives represent more than 50 % of all the drugs in clinical use of the world. Higher plants contribute not less than 25 % of the total. Almost 60 % of drugs approved for cancer treatment are of natural origin.

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Although marine compounds are underrepresented in current pharmacopoeia, it is anticipated that the marine environment will become an invaluable source of novel compounds in the future [2].

Marine nutraceuticals can be derived from a vast array of sources, including marine plants, microorganisms, and sponges. Marine nutraceutical products currently promoted to various countries include fish oil, chitin, chitosan, marine enzymes and chondroitin from shark cartilage, sea cucumbers and mussels. Polysaccharides derived from alga, including alginate, carrageenan and agar are widely used as thickeners and stabilizers in a variety of food ingredients. In addition, Omega PUFA (Polyunsaturated fatty acid) is an important ingredient to the nutraceutical industry [3]. It has been proven that Omega-PUFA, especially eicosapentaenoic acid (EPA) and docosahexenoic acid (DHA) play a significant role in number of aspects of human health [4].

More than 70% of our planet's surface is covered by oceans. An exciting "marine pipeline" of new anticancer clinical and preclinical agents has emerged from intense efforts over the past decade to more effectively explore the rich chemical diversity offered by marine life. The chemical adaptations generally take the form of so-called "secondary metabolites," and involve such well known chemical classes as terpenoids, alkaloids, polyketides, peptides, shikimic acid derivatives, sugars, steroids, and a multitude of mixed biogenesis metabolites. In addition, and unique to the marine environment, is the relatively common utilization of covalently bound halogen atoms in secondary metabolites, mainly chlorine and bromine, presumably due to their ready availability in seawater [5, 6]. Marine compounds that act as hallmarks of cancer presented namely self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replication, sustained angiogenesis and tissue invasion and metastasis [7–11].

1.2 Sponges

Marine sponges for the past decades have been considered as a very fertile field for the discovery of bioactive natural chemical substances with respect to the diversity of their primary and secondary chemical components and metabolites. Marine sponges (Porifera) are the oldest metazoan group, having an outstanding importance as a living fossil [12]. There are approximately 8000 described species of sponges and perhaps twice as many un-described species [13, 14]. Sponges inhabit every type of marine environment, from polar seas to temperate and tropical waters and also thrive and prosper at all depths. They show an amazing variety of shapes, sizes and colours. Giant barrel sponges can reach up to 70 in. in height, while another tiny encrusting sponge may only be half of an inch long. Sponges are sessile organisms. However, due to their cellular plasticity, many sponges reorganize their bodies continuously and move during this process very slowly [14]. Marine sponges through evolutionary and ecological long term changes often contain diverse microbial communities (bacteria, archaea, microalgae, fungi) which comprise as much as 40% of the sponge volume and can contribute significantly to host metabolism

(e.g., via photosynthesis or nitrogen fixation). The ecological and evolutionary importance of sponge-microbe associations can be mirrored by their enormous biotechnological potential producing a great range of bioactive metabolites [15, 16]. Scientist has discovered more than 5000 species and also there are more than 8000 marine sponges on Earth.

Marine sponges have been ranked at the top with respect to the discovery of bioactive compounds with potential pharmaceutical applications. The diversity in chemical structures of sponge-derived metabolites is related to an equally diverse pattern of activities. The chemical diversity of sponge natural products is remarkable, including unusual nucleosides, bioactive terpenes, sterols, cyclic peptides, alkaloids, fatty acids, peroxides, and amino acid derivatives (which are frequently halogenated) [17]. In the field of natural products chemistry and research suggest that sponges have the potential to provide future drugs against some important diseases, such as viral diseases, malaria, inflammations, immunosuppressive diseases and various malignant neoplasms [5, 18–20]. In the last few years there are several other candidates from marine natural compounds in the pipeline for evaluation in Phase I–III clinical trials for the treatment of various cancers [21, 22]. From the previous studies, marine natural compounds from sponge species were undergoing preclinical and clinical trials (I, II, III) for anticancer activity. Among the compounds were discodermolide, hemiasterlins A & B, modified halichondrin B, KRN-70000, Alipkinidine (alkaloid), fascaphysins (alkaloid), isohomohalichondrin B, Halichondrin B, Laulimalide/Fijianolide, 5-methoxyamphimedine (alkaloid) and Variolin (alkaloid) [16]. In recent years, new marine-derived antiangiogenic agents have been widely investigated. At least 43 marine-derived natural products and their derivatives have been reported to display antiangiogenic activities, mediated by distinct or unknown molecular mechanisms [16, 23].

The first successful sponge-derived pharmaceutical drugs were the nucleosides spongothymidine and spongouridine which were isolated from *Tectitethya crypta* [24]. A derivative of these nucleosides, Ara-C (also known as 1-beta-D-Arabinofuranosylcytosine or cytarabine) is documented as the first marine derived anticancer agent that is recently used for the treatment of leukemia [25, 26]. An overview (2011) retrieved scientific papers identifying 39 compounds from marine sponges with apoptosis-inducing anticancer properties [27]. Renieramycins are members of the tetrahydroiso-quinoline family that were isolated from marine sponges belonging to genera *Reniera* induces apoptosis through p53-dependent pathway and may inhibit progression and metastasis of lung cancer cells [28]. Monanchocidin is a novel polycyclic guanidine alkaloid isolated from the marine sponge *Monanchora pulchra* that promote cell death in human monocytic leukemia (THP-1), human cervical cancer (HeLa) and mouse epidermal (JB6 Cl41) cells [29]. Smenospongine, a sesquiterpene aminoquinone, from the sponge *Smenospongia* sp. have antiproliferetive and antiangiogenic activities [30]. The macrocyclic lactone polyether spongistatin 1 was isolated from the marine sponge *Spongia* sp. [31], inhibit mitosis, microtubule assembly and inducing cytotoxic cell death in numerous cancer cell lines [32]. Recently, scientists purified a lectin from the marine sponge *Cinachyrella apion* (CaL) have hemolytic, cytotoxic and antiproliferative proper-

ties and cell death in tumor cells [33]. Heteronemin, a marine sesterterpene isolated from the sponge *Hyrtios* sp., inhibits chronic myelogenous leukemia cells by regulating cell cycle, apoptosis, mitogen-activated protein kinases (MAPKs) pathway and the nuclear factor kappaB (NF-kappaB) signaling cascade [34]. Still there are number of anticancer compounds is isolated and screened form marine sponges.

1.3 Algae

Algae are relatively undifferentiated organisms which, unlike plants, have no true roots, leaves, flowers or seeds. They are found in marine, freshwater and terrestrial habitats. Their size varies from tiny microscopic unicellular forms of 3–10 μm (microns) to large macroscopic multicellular forms up to 70 m long and growing at up to 50 cm per day. Most of the algae are photosynthetic organisms that have chlorophyll. Marine macroalgae are important ecologically and commercially to many regions of the world, especially in Asian countries such as China, Japan and Korea [35]. Phytoplankton, seaweeds and symbiotic dinoflagellates (unicellular, biflagellate organisms) in corals and sea anemones are marine algae. Seaweeds are classified as green algae (Chlorophyta), brown algae (Phaeophyta), red algae (Rhodophyta) and some filamentous blue-green algae (Cyanobacteria). Most of the seaweeds are red (6000 species) and the rest known are brown (2000 species) or green (1200 species). Seaweeds are used in many maritime countries as a source of food, for industrial applications and as a fertilizer. Industrial utilization is at present largely confined to extraction for phycocolloids, industrial gums classified as agars, carrageenans and alginates. Carrageenans, extracted from red seaweeds such as Chondrus, Gymnogongrus, and Eucheuma among others, are used to provide particular gel qualities. Alginates are derivatives of alginic acid extracted from large brown algae such as Laminaria. They are used in printers' inks, paints, cosmetics, insecticides, and pharmaceutical preparations.

Seaweeds have been one of the richest and most promising sources of bioactive primary and secondary metabolites [36]. The algae synthesize a variety of compounds such as carotenoids, terpenoids, xanthophylls, chlorophyll, vitamins, saturated and polyunsaturated fatty acids, amino acids, acetogenins, antioxidants such as polyphenols, alkaloids, halogenated compounds and polysaccharides such as agar, carrageenan, proteoglycans, alginate, laminaran, rhamnan sulfate, galactosyl glycerol and fucoidan [36, 37]. These compounds probably have diverse simultaneous functions for the seaweeds and can act as various functions including anticancer effects. The seaweeds are the rich source of carotenoids, the most notable being β-carotene, α-carotene, fucoxanthin, astaxanthin, canthaxanthin, zeaxanthin and lutein has been reported as effective antioxidants. Seaweed carotenoids are powerful antioxidants associated with the prevention of cardiovascular, neurodegenerative diseases and also cancer. The carotenoids have been extensively studied and the consumption of the dietary carotenoids has been correlated with cancer prevention [38, 39]. Also, amelioration effect of green sea algae derived compound

dimethylsulfonioacetate (DMSP) has shown that on stress and aging closely related to cancer, solid and free cell cancer, and neural degeneration caused by brain cancer with model animals.

1.4 Microbes

Microbes, like this single-celled marine phytoplankton, make up a staggering 90%of the ocean's total biomass. Marine microbes are tiny organisms that live in marine environments and can only be seen under a microscope. They include cellular life forms such as bacteria, fungi and plankton along with the viruses that freeload on the cellular life forms. There are more than a billion micro-organisms living in each litre of seawater, and it is now known that microbes dominate the abundance, diversity and metabolic activity of the ocean. Marine microbes are having huge biochemical diversity and rich source of novel drugs. Marine microbial compounds are an important source for drug development [40]. Marine bacteria are one of the important sources for many bioactive compounds, antibiotics and pharmaceuticals. They are usually found in the marine sediments and also found to be associated with the marine organisms [41]. Despite a limited number of marine microbial antitumor agents currently on the market or in clinical trials, there are strong evidences that some promising marine natural compounds in clinical trials as well as some approved marine-derived anticancer agents produced by invertebrates, in fact metabolic products of their associated microorganisms, or derived from a diet of prokaryotic microorganisms [42, 43].

Meroterpenoids are a class of secondary metabolites in which the terpenoid moieties are linked to molecules from different biosynthetic pathways. Meroterpenoids containing quinones are also widespread in marine microorganisms, with prenylated naphtoquinones and reduced hydroquinone analogues are reported from marine microorganisms especially fungi and actinomycetes [44]. Meroterpenoids especially those with anticancer activity, produced by all types of marine-derived microorganisms. Marine fungi are also reported as a potential source for bioactive compounds. Polyketide synthases are a class of enzymes that are involved in the biosynthesis of secondary metabolites. The microbe's derived compounds are potential use for anticancer research.

Actinomycetes are one of the most efficient groups of secondary metabolite producers, they exhibit a wide range of biological activities and also anticancer effects. Several species have been isolated and screened from the soil in the past decades. Among its various genera, *Streptomyces, Saccharopolyspora, Amycolatopsis, Micromonospora* and *Actinoplanes* are the major producers of commercially important biomolecules [45]. Actinomycetes are virtually unlimited sources of new compounds with many therapeutic applications and hold a prominent position due to their diversity and proven ability to produce novel bioactive compounds [46]. In the search for bioactive compounds from actinomycetes collected from the deep-sea water in Toyama Bay, two new glycosylated polyketides were isolated from the

culture extract of *Micromonospora* sp., the arisostatin A and arisostatin B, respectively [47, 48]. Arisostatins are the new members of tetrocarcin-type cytotoxic compounds. Arisostatin A showed a potent cytotoxic effect on human cancer cells and activates caspase 3, a key effector protease responsible for apoptosis induction [49].

Marine fungi have proven to be untapped resources for the rich and promising source of novel antibacterial, antiplasmodial, anti-inflammatory antiviral and anticancer agents. Most of the fungi grow in unique and extreme environments therefore they have the ability to generate unique and unusual secondary metabolites [50]. Toluquinol is derived from marine fungus interferes with one of the hallmarks of cancer described by Hanahan and Weinberg by impairing the unlimited replicative potential, characteristic of tumor cells. Toluquinol represses the proliferation of the promyelocytic leukemia HL60 cell line, fibrosarcoma HT1080 cell line and colon adenocarcinoma HT29 cell line. The IC50 values, which represent the concentrations of toluquinol yielding a 50 % of cell growth, were lower than 10 μM in the three cell lines and also inhibits angiogenesis of cancer [51]. Diketopiperazines (DKPs) of marine resources, especially those isolated from marine-derived fungi, have been paid increasing attention for their diversity in chemical structure and bioactivity. Halimide ((-)-phenylahistin) is a fungal prenylated DKP isolated from *Aspergillus ustus* NSC-F038 and arrested the cancer cell cycle of P388 in the G2/M phase [52].

1.5 Tunicates

Tunicates are also known as *urochordates,* belong to the subphylum Tunicata or Urochordata. Tunicates have been shown as a primitive model organism to study immunodefense since the innate immune system has been hypothesized as an important functional component that may partially explain the lack of metastatic tumors in invertebrates [53]. Marine-derived compounds have reached clinical trials as antitumor from tunicates such as didemnin B, Aplidine, and ecteinascidin 743. Didemnin B (DB), a cyclic depsipeptide from the compound tunicate *Tridemnum solidum*, was the first marine-derived compound to enter Phases I and II clinical trials. The Phase II studies, sponsored by the U. S. National Cancer Institute, indicated complete or partial remissions with non-Hodgkins lymphoma, but cardiotoxicity caused didemnin B to be dropped from further study. The closely related dehydrodidemnin B (DDB, Aplidine) was isolated in 1988 from a second colonial tunicate, *Aplidium albicans*, and spectroscopic studies assigned a structural formula in which a pyruvyl group in DDB replaced the lactyl group in DB and syntheses of DDB have been achieved. Aplidine is more active than DB and lacks DB's cardiotoxicity. The second family of tunicate-derived antitumor agents are the ecteinascidins (ETs), from the mangrove tunicate *Ecteinascidia turbinata*. The antitumor extracts of *E. turbinata* were first described in 1969, but the small amount of ETs in *E. turbinate* prevented their isolation for over a decade. Phase II clinical trials with ET 743 are underway [54].

1.6 Miscellaneous

In recent years, marine natural product bioprospecting has yielded a considerable number of drug candidates. Research into the ecology of marine natural products has shown that many of these compounds have anticancer function [43]. Apart from sponge, algae, tunicate, microbes other marine organisms include sea cucumber, sear hare, mollusks and Bryozoans derived marine natural products also has a anticancer function include microtubule-interfering agents, DNA-interactive agents, phosphatase inhibitors *etc*. Alkaloids pyridoacridines isolated from various marine sources have been reported to possess significant cytotoxicity against cultured cells, and the family as a whole seems to be of great interest as a source of new lead structures for the development of future generation of therapeutic agents [55]. Sea cucumbers are one of the marine animals which are important as human food source, and sea cucumber extracts have been used for over-the-counter dietary health supplements [56, 57]. Triterpene glycosides from sea cucumbers demonstrate that wide spectrum of biological effects, such as antifungal, antitumor, hemolytic, cytostatic, pro-apoptotic and immunomodulatory activities. Frondoside A and Cucumariosides showed cancer preventive effects on both *in vitro* and *in vivo* models [58–60]. The dolastatins were originally reported from the Indian Ocean sea hare, *Dolabella auricularia*. Subsequently, a number of dolastatins and related molecules were isolated from filamentous marine cyanobacteria, which are the natural diet of the sea hares [61]. The dolastatins is the most active molecule in inhibiting cancer cell growth [62].

Meroterpenes are a class of natural products that exhibit a remarkable chemical diversity. This rich chemistry is a consequence of their mixed biosynthesis, as they are composed of an aromatic moiety/carbohydrate residue and also a terpenoid portion that can range from one to nine isoprene units. Prenylated quinone/hydroquinone derivatives are amongst the most numerous and widespread in marine environment [63, 64]. Meroterpenes are not exclusive to marine organisms, being found also in many terrestrial species. This type of compounds has various biological functions including anticancer effects. In the marine environment, the main sources of meroterpenes are brown algae, microorganisms, soft corals and marine invertebrates, such as sponges or ascidians [64]. Number of bacteria and cyanobacteria associated with the marine sponges have been found to be the sources of antibiotics and other bioactive compounds and it has been reported that the wider biosynthetic capabilities of sponges are associated with their symbiotic microorganisms [65]. IB-96212, a 26-membered macrolide that contains a spiroketal lactone structure, is produced by the actinomycete, *Micromonospora* sp. L-25-ES25-008, isolated from a sponge, collected from the Indian Ocean near the coast of Mozambique [66] and showed cytotoxic activity against mouse leukemia P-388 and human lung nonsmall cell A-549, colon adenocarcinoma HT-29 and melanoma MEL-28 cell lines [67]. Cembrane-type diterpenoids are a large and structurally varied group of natural products isolated from both terrestrial and marine organisms [68]. In the marine environment, coelenterates of the orders Alcyonacea and Gorgonacea are recognized as the most prominent source of cembranoids, which usually exhibit cyclic

ether, lactone, or furane moieties around the cembrane framework [69–71]. The diterpenoids of the cembrane family have been shown to biomedical perspective, cytotoxicity is the most remarkable property of this class of diterpenoids [72].

1.7 Research Scope

Marine environments play a vital role in exploring and studying various marine resources and isolation, characterization and applications of biological active compounds from marine field. The sea covers over 70 % of the earth's surface and large proportion of the sea offers untapped sources of potential drugs with promising activities due to a large diversity of marine habitats and environmental conditions (nutrient availability, sunlight presence, and salinity levels). In the area of marine research, a recent census of marine life that involved the participation of 2700 scientists from over 80 nations assessed the diversity, distribution and abundance of marine life resulted in the discovery of over 6000 potentially novel species (Census of marine life. http://www.comlorg/about-census).

The anticancer research progress in throughout the world including Republic of Korea, Japan, India, China, Singapore, Malaysia, Australia and USA, as well as others countries also in importance as a research priority for finding new anticancer compounds from marine sources. However, advances in drug discovery are expected to encourage applications from the marine field. A major task of marine is to develop an efficient process for the discoveries of novel molecules from the marine environment. The huge level of marine biodiversity of marine organism makes them a prime target for the productions of enzymes and bioactive molecules for the treatment of various diseases including cancer. Biochemical studies of marine organisms are an important task for the discovery of new drug molecules and biological tools and management of biodiversity. These research efforts, it is clear that the marine environment represents an important source of unknown natural compounds whose medicinal potential must be evaluated. Almost 50 % of the antitumor agents approved in the last 50 years of the twentieth century were either compounds derived from natural sources or (semi-) synthetic analogs of these products. Natural compounds remain a high output source of promising chemotherapeutic or chemopreventive agents in current cancer research. In addition to PharmaMar, other pharmaceutical companies including Bedford, Enzon, Eisai Inc., Novartis, Aventis, Eli Lilly, Abbott In"azyme, Pfizer and Taiho Pharmaceuticals Co., have therapeutic compounds of marine origin under development.

1.8 Organization of Handbook

This handbook combines the knowledge about the compounds isolated from sponge, algae, microbes, tunicatesetc and also methods, product development, industrial and biomedical applications. This handbook is divided into five parts. The first part of

the book comprises the introduction, sponges, microbes, algae, tunicates and other miscellaneous compounds derived from other marine organisms. The second part deals with sponge derived drug discovery represent one of the most promising sources of leads in the research of new cancer drugs. These chapters provide an overview of the angiogenesis inhibitors isolated from marine sponges based on the available information regarding their primary targets or mechanism of action and antitumour effect of triterpenoids, cyclic peptides and cyclodepsipeptides also discussed. Moreover, marine sponge derived compound eribulin with respect to its clinical pharmacology, pharmacokinetics, pharmacodynamics, mechanism of action, metabolism, preclinical studies and clinical trials. The third part of the book introduces about the marine algae derived compounds on cancer targets. In this amelioration and anti tumor effect of a tertiary sulfonium compound, dimethylsulfoniopropionate, from green sea algae and the various biological functions including anticancer effects of the seaweed carotenoids such as fucoxanthin etc. and the possible mechanisms of action are described. Fucoidan, a sulfated polysaccharides isolated from brown algae, anticancer and antimetastatic action are described. The health benefits of marine algae have been intensively investigated for human. The seaweeds biological roles and potential benefits for female cancers to be discussed in this part.

The fourth part of the book provides the details about marine microbial derived compounds for cancer therapeutics. In this chapter provide evidence on the antitumor compounds isolated from marine microbes such as fungai, bacteria and actinobacteria. The fifth part of the book dealt with marine tunicate derived compounds for cancer therapeutics. Finally the sixth part of the book covers others marine organisms derived compounds for cancer to be discussed. In this part deals the structures and sources of the isolated marine pyridoacridine alkaloids, as well as the mechanisms underlying the cytotoxicity of certain naturally occurring marine pyridoacridines. Anticancer effects of triterpene glycosides, Frondoside A and Cucumarioside A2–2 isolated from sea cucumbers. Discovery and computer-aided drug design studies of the anticancer marine triterpene sipholanes as novel P-gp and Brk modulators. Molecular targets of anticancer agents from filamentous marine cyanobacteria. Cytotoxic terpene-purines and terpene-quinones from the sea cytotoxic triterpene glycosides from sea cucumbers. Meroterpenes from marine invertebrates chemistry and application in cancer. Marine sponge derived actinomycetes and their anticancer compounds. Advances of microtubule-targeting small molecular anticancer agents from marine origin. Targeting cellular proapoptotic agents from marine sources. Cytotoxic cembrane diterpenoids. Pederin, psymberin and the structurally related mycalamides biological activities, P-gp inhibitory activity from marine sponges, tunicates and algae.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA: Can J Clin 61(2):69–90
2. Jimeno J, Faircloth G, Sousa-Faro J, Scheuer P, Rinehart K (2004) New marine derived anticancer therapeutics—a journey from the sea to clinical trials. Mar Drugs 2(1):14–29

3. Rasmussen RS, Morrissey MT (2007) Marine biotechnology for production of food ingredients. Adv Food Nutr Res 52:237–292
4. Venegas-Calerón M, Sayanova O, Napier JA (2010) An alternative to fish oils: metabolic engineering of oil-seed crops to produce omega-3 long chain polyunsaturated fatty acids. Prog Lipid Res 49(2):108–119
5. Simmons TL, Andrianasolo E, McPhail K, Flatt P, Gerwick WH (2005) Marine natural products as anticancer drugs. Mol Cancer Ther 4(2):333–342
6. Firn RD, Jones CG (2003) Natural products-a simple model to explain chemical diversity. Nat Prod Rep 20(4):382–391
7. Schumacher M, Kelkel M, Dicato M, Diederich M (2011) Gold from the sea: marine compounds as inhibitors of the hallmarks of cancer. Biotechnol Adv 29(5):531–547
8. Orhan I, Şener B, Kaiser M, Brun R, Tasdemir D (2010) Inhibitory activity of marine sponge-derived natural products against parasitic protozoa. Mar Drugs 8(1):47–58
9. Dalisay DS, Morinaka BI, Skepper CK, Molinski TF (2009) A tetrachloro polyketide hexahydro-1H-isoindolone, muironolide A, from the marine sponge Phorbas sp. natural products at the nanomole scale. J Am Chem Soc 131(22):7552
10. Proksch P, Putz A, Ortlepp S, Kjer J, Bayer M (2010) Bioactive natural products from marine sponges and fungal endophytes. Phytochem Rev 9(4):475–489
11. Kramer A (2011) Identification, bioactivity and biosynthesis of natural products from marine sponge associated fungi.
12. Müller WE (1998) Origin of Metazoa: sponges as living fossils. Naturwissenschaften 85(1):11–25
13. Hooper JN, Van Soest RW (2002) Systema Porifera. A guide to the classification of sponges. Springer, Berlin
14. Thakur NL, Müller WE (2004) Biotechnological potential of marine sponges. Curr Sci 86(11):1506–1512
15. Taylor MW, Radax R, Steger D, Wagner M (2007) Sponge-associated microorganisms: evolution, ecology, and biotechnological potential. Microbiol Mol Bio Rev 71(2):295–347
16. Perdicaris S, Vlachogianni T, Valavanidis A (2013) Bioactive natural substances from marine sponges: new developments and prospects for future pharmaceuticals. Nat Prod Chem Res 1(3):1–8
17. Villa FA, Gerwick L (2010) Marine natural product drug discovery: leads for treatment of inflammation, cancer, infections, and neurological disorders. Immunopharmacol Immunotoxicol 32(2):228–237
18. Alcaraz M, Paya M (2006) Marine sponge metabolites for the control of inflammatory diseases. Curr Opin Invest Drugs 7(11):974
19. Molinski TF, Dalisay DS, Lievens SL, Saludes JP (2008) Drug development from marine natural products. Nat Rev Drug Discovery 8(1):69–85
20. Gordaliza M (2010) Cytotoxic terpene quinones from marine sponges. Mar Drugs 8(12):2849–2870
21. Mayer A, Rodríguez AD, Berlinck RG, Fusetani N (2011) Marine pharmacology in 2007–8: marine compounds with antibacterial, anticoagulant, antifungal, anti-inflammatory, antimalarial, antiprotozoal, antituberculosis, and antiviral activities; affecting the immune and nervous system, and other miscellaneous mechanisms of action. Comp Biochem Physiol C: Toxicol Pharmacol 153(2):191–222
22. Mayer A, Glaser KB, Cuevas C, Jacobs RS, Kem W, Little RD, McIntosh JM, Newman DJ, Potts BC, Shuster DE (2010) The odyssey of marine pharmaceuticals: a current pipeline perspective. Trends Pharmacol Sci 31(6):255–265
23. Wang Y-Q, Miao Z-H (2013) Marine-derived angiogenesis inhibitors for cancer therapy. Mar Drugs 11(3):903–933
24. Bergmann W, Feeney RJ (1950) The isolation of a new thymine pentoside from sponges1. J Am Chem Soc 72(6):2809–2810
25. Proksch P, Edrada R, Ebel R (2002) Drugs from the seas-current status and microbiological implications. Appl Microbiol Biotech 59(2–3):125–134
26. Schwartsmann G (2000) Marine organisms and other novel natural sources of new cancer drugs. Ann Oncol 11(suppl 3):235–243

27. Essack M, Bajic VB, Archer JA (2011) Recently confirmed apoptosis-inducing lead compounds isolated from marine sponge of potential relevance in cancer treatment. Mar Drugs 9(9):1580–1606
28. Halim H, Chunhacha P, Suwanborirux K, Chanvorachote P (2011) Anticancer and antimetastatic activities of renieramycin M, a marine tetrahydroisoquinoline alkaloid, in human non-small cell lung cancer cells. Anticancer Res 31(1):193–201
29. Guzii AG, Makarieva TN, Denisenko VA, Dmitrenok PS, Kuzmich AS, Dyshlovoy SA, Krasokhin VB, Stonik VA (2010) Monanchocidin: a new apoptosis-inducing polycyclic guanidine alkaloid from the marine sponge *Monanchora pulchra*. Org Lett 12(19):4292–4295
30. Kondracki M-L, Guyot M (1987) Smenospongine: a cytotoxic and antimicrobial aminoquinone isolated from *Smenospongia sp*. Tetrahedron Lett 28(47):5815–5818
31. Kong D, Yamori T, Kobayashi M, Duan H (2011) Antiproliferative and antiangiogenic activities of smenospongine, a marine sponge sesquiterpene aminoquinone. Mar Drugs 9(2):154–161
32. Bai R, Cichacz ZA, Herald CL, Pettit GR, Hamel E (1993) Spongistatin 1, a highly cytotoxic, sponge-derived, marine natural product that inhibits mitosis, microtubule assembly, and the binding of vinblastine to tubulin. Mol Pharmacol 44(4):757–766
33. Rabelo L, Monteiro N, Serquiz R, Santos P, Oliveira R, Oliveira A, Rocha H, Morais AH, Uchoa A, Santos E (2012) A lactose-binding lectin from the marine sponge *Cinachyrella apion* (Cal) induces cell death in human cervical adenocarcinoma cells. Mar Drugs 10(4):727–743
34. Schumacher M, Cerella C, Eifes S, Chateauvieux S, Morceau F, Jaspars M, Dicato M, Diederich M (2010) Heteronemin, a spongean sesterterpene, inhibits TNFα-induced NF-κB activation through proteasome inhibition and induces apoptotic cell death. Biochem Pharmacol 79(4):610–622
35. Smit AJ (2004) Medicinal and pharmaceutical uses of seaweed natural products: a review. J Appl Phycol 16(4):245–262
36. Faulkner DJ (2001) Marine natural products. Nat Prod Rep 18(1):1R–49R
37. De Almeida CLF, Falc DS, Lima DM, Gedson R, Montenegro DA, Lira NS, De Athayde-Filho PF, Rodrigues LC, De Souza MdF, Barbosa-Filho JM (2011) Bioactivities from marine algae of the genus Gracilaria. Int J Mol Sci 12(7):4550–4573
38. Holick CN, Michaud DS, Stolzenberg-Solomon R, Mayne ST, Pietinen P, Taylor PR, Virtamo J, Albanes D (2002) Dietary carotenoids, serum β-carotene, and retinol and risk of lung cancer in the Alpha-Tocopherol, Beta-Carotene cohort study. Am J Epidemiol 156(6):536–547
39. Rock CL (2003) Carotenoid update. J Am Diet Assoc 103(4):423–425
40. Imhoff JF, Labes A, Wiese J (2011) Bio-mining the microbial treasures of the ocean: new natural products. Biotechnol Adv 29(5):468–482
41. Thakur NL, Hentschel U, Krasko A, Pabel CT, Anil AC, Müller WE (2003) Antibacterial activity of the sponge Suberites domuncula and its primmorphs: potential basis for epibacterial chemical defense. Aquat Microb Ecol 31(1):77–83
42. Gerwick WH, Fenner AM (2012) Drug discovery from marine microbes. Microb Ecol 65:1–7
43. Haefner B (2003) Drugs from the deep: marine natural products as drug candidates. Drug Discov Today 8(12):536–544
44. Sunassee SN, Davies-Coleman MT (2012) Cytotoxic and antioxidant marine prenylated quinones and hydroquinones. Nat Prod Rep 29(5):513–535
45. Solanki R, Khanna M, Lal R (2008) Bioactive compounds from marine actinomycetes. Indian J Microbiol 48(4):410–431
46. Subramani R, Aalbersberg W (2012) Marine actinomycetes: an ongoing source of novel bioactive metabolites. Microbiol Res 167:571–580
47. Igarashi Y, Takagi K, Kan Y, Fujii K, Harada K-i, Furumai T, Oki T (2000) Arisostatins A and B, new members of tetrocarcin class of antibiotics from Micromonospora sp. TP-A0316. II. Structure determination. J Antibiot 53(3):233–240

48. Furumai T, Takagi K, Igarashi Y, Saito N, Oki T (2000) Arisostatins A and B, new members of tetrocarcin class of antibiotics from Micromonospora sp. TP-A0316. I. Taxonomy, fermentation, isolation and biological properties. J Antibiot 53(3):227
49. Kim Y-H, Shin HC, Song DW, Lee S-H, Furumai T, Park J-W, Kwon TK (2003) Arisostatins A induces apoptosis through the activation of caspase-3 and reactive oxygen species generation in AMC-HN-4 cells. Biochem Biophys Res Commun 309(2):449–456
50. Fenical W, Jensen PR (1993) Marine microorganisms: a new biomedical resource. Mar Biotechnol 1:419–457
51. García-Caballero M, Cañedo L, Fernández-Medarde A, Medina MÁ, Quesada AR (2014) The marine fungal metabolite, AD0157, inhibits angiogenesis by targeting the Akt signaling pathway. Mar Drugs 12(1):279–299
52. Kanoh K, Kohno S, Asari T, Harada T, Katada J, Muramatsu M, Kawashima H, Sekiya H, Uno I (1997) (–)-Phenylahistin: a new mammalian cell cycle inhibitor produced by *Aspergillus ustus*. Bioorg Med Chem Lett 7(22):2847–2852
53. Cooper EL, Mansour M, Negm H (1996) Marine invertebrate immunodefense responses: molecular and cellular approaches in tunicates. Ann Rev Fish Dis 6:133–149
54. Rinehart KL (2000) Antitumor compounds from tunicates. Med Res Rev 20(1):1–27
55. Delfourne E, Bontemps-Subielos N, Bastide J (2000) Structure revision of the marine pentacyclic aromatic alkaloid: cystodamine. Tetrahedron Lett 41(20):3863–3864
56. Stonik V, Kalinin V, Avilov S (1999) Toxins from sea cucumbers (holothuroids): chemical structures, properties, taxonomic distribution, biosynthesis and evolution. J Nat Toxins 8(2):235–248
57. Janakiram NB, Mohammed A, Zhang Y, Choi C-I, Woodward C, Collin P, Steele VE, Rao CV (2010) Chemopreventive effects of frondanol A5, a cucumaria frondosa extract, against rat colon carcinogenesis and inhibition of human colon cancer cell growth. Cancer Prev Res 3(1):82–91
58. Tong Y, Zhang X, Tian F, Yi Y, Xu Q, Li L, Tong L, Lin L, Ding J (2005) Philinopside a, a novel marine derived compound possessing dual anti-angiogenic and anti-tumor effects. Int J Cancer 114(6):843–853
59. Tian F, Zhang X, Tong Y, Yi Y, Zhang S, Li L, Sun P, Lin L, Ding J (2005) PE, a new sulfated saponin from sea cucumber, exhibits anti-angiogenic and anti-tumor activities in vitro and in vivo. Cancer Biol Ther 4(8):874–882
60. Aminin D, Chaykina E, Agafonova I, Avilov S, Kalinin V, Stonik V (2010) Antitumor activity of the immunomodulatory lead Cumaside. Int Immunopharmacol 10(6):648–654
61. Luesch H, Moore RE, Paul VJ, Mooberry SL, Corbett TH (2001) Isolation of dolastatin 10 from the marine cyanobacterium Symploca species VP642 and total stereochemistry and biological evaluation of its analogue symplostatin 1. J Nat Prod 64 (7):907–910
62. Bai R, Verdier-Pinard P, Gangwar S, Stessman CC, McClure KJ, Sausville EA, Pettit GR, Bates RB, Hamel E (2001) Dolastatin 11, a marine depsipeptide, arrests cells at cytokinesis and induces hyperpolymerization of purified actin. Mol Pharmacol 59(3):462–469
63. Zubia E, Ortega MJ, Salva J (2005) Natural products chemistry in marine ascidians of the genus Aplidium. Mini-Rev Org Chem 2(4):389–399
64. Menna M, Imperatore C, D'Aniello F, Aiello A (2013) Meroterpenes from marine invertebrates: structures, occurrence, and ecological implications. Mar Drugs 11(5):1602–1643
65. Anand TP, Bhat AW, Shouche YS, Roy U, Siddharth J, Sarma SP (2006) Antimicrobial activity of marine bacteria associated with sponges from the waters off the coast of South East India. Microbiol Res 161(3):252–262
66. Canedo LM, Fernández-Puentes JL, Baz JP (2000) IB-96212, a novel cytotoxic macrolide produced by a marine *Micromonospora*. II. Physico-chemical properties and structure determination. J Antibiot 53(5):479
67. Fernandez-Chimeno RI, Canedo L, Espliego F, Grávalos D, De La Calle F, Fernández-Puentes JL, Romero F (2000) IB-96212, a novel cytotoxic macrolide produced by a marine

Micromonospora. I. Taxonomy, fermentation, isolation and biological activities. J Antibiot 53(5):474–478
68. Yang B, Zhou X-F, Lin X-P, Liu J, Peng Y, Yang X-W, Liu Y (2012) Cembrane diterpenes chemistry and biological properties. Curr Org Chem 16(12):1512–1539
69. Qin S, Huang H, Guo YW (2008) A new cembranoid from the Hainan soft coral *Sinularia* sp. J Asian Nat Prod Res 10:1075–1079. doi:10.1080/10286020802319410
70. Rodriguez AD, Shi JG (1998) The first cembrane-pseudopterane cycloisomerization. J Org Chem 63:420–421
71. Sponholtz WR, Bianco MA, Gribble GW (2008) Isolation and structure determination of the cembranoid eunicin from a new genus of octocoral, *Pseudoplexaura*. Nat Prod Rep 22:441–448
72. Sawant SS, Sylvester PW, Avery MA, Desai P, Youssef DTA, El Sayed KA (2004) Bioactive rearranged and halogenated semisynthetic derivatives of the marine natural product sarcophine. J Nat Prod 67:2017–2023. doi:10.1021/np0497393