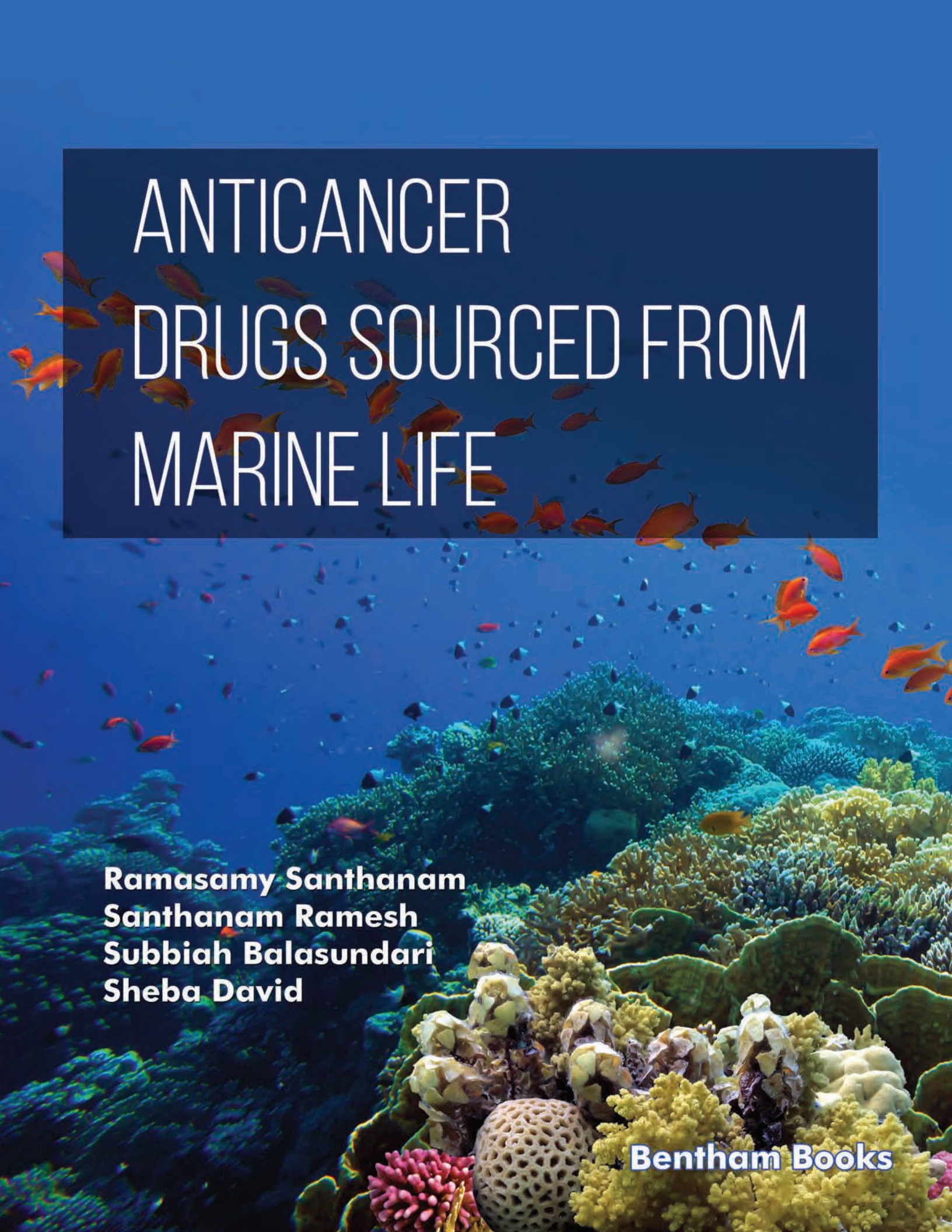
ANTICANCER DRUGS SOURCED FROM MARINE LIFE



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Medicinal Chemistry and Marine Life

(Volume 1)

Anticancer Drugs Sourced from Marine Life

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(Volume 1)

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FOREWORD

I am very much pleased to write my Foreword for this inter-disciplinary title "Medicinal Chemistry and Marine Life: Anticancer Drugs Sourced from Marine Life" relating to an untouched aspect of Fisheries and Pharmaceutical disciplines.

Cancer is an increasing public health hazard and about 60% of the anticancer drugs of natural origin are presently in use to treat this disease. Owing to the tumor cells resistance to drugs, and undesirable side effects observed with the synthetic drugs, there is an urgent need for the development of new anticancer drugs. In this regard, the marine environment, an exceptional reservoir of anticancer compounds, has paved way for further investigations on the utilization of its vast biodiversity. Comparing with terrestrial organisms, marine organisms do not have a distinguished history of use in traditional medicine. But during the last 50 years, advances in new technologies and engineering opened up the marine environment to large scale scientific exploration. Despite considerable challenges, 11 marine biota-derived anticancer drugs arrived in the market and are currently used in therapeutics.

The present title, first of its kind deals with the major constituents of marine life with promising anticancer compounds and in my opinion, this publication could serve as a potential resource for teachers and students of both Marine and Pharmaceutical Sciences besides serving as a reference for anticancer agents from marine source.

I congratulate the authors for their timely contribution.

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PREFACE

Cancer remains one of the most life-threatening diseases and its prevalence is increasing worldwide especially in countries that are witnessing urbanization and rapid industrialization changes. In 2018 alone, about 18 million new cases of cancer were reported globally, resulting in approximately 10 million deaths. Cancer treatments do not have potent medicine as the currently available drugs are causing side effects in some instances. Hence, identifying novel effective drugs is urgently needed, and many ongoing research programs are in the process of identifying new anti-cancer drugs from marine organisms which are considered "blue drug banks" of unique anti-cancer compounds with diverse groups of chemical structures. Seven marine-based pharmaceuticals have so far been approved for marketing; 23 compounds are in clinical trials between phases I and III; and over one thousand compounds isolated from marine organisms are undergoing preclinical studies. It is worthy of mention here that among those marine organism-derived compounds in clinical use, four compounds viz. cytarabine (Cytosar®), trabectedin (Yondelis®), eribulin mesylate (Halaven®) and the conjugated antibody brentuximab vedotin (Acentris®) are used in the treatment of cancer.

Though a few books are presently available on marine natural products and pharmaceutical marine life, a comprehensive volume dealing with the biodiversity of marine organisms yielding anticancer compounds has not so far been published. This interdisciplinary publication first of its kind would answer this long-felt need. It deals mainly with the ecology, and biology of marine organisms yielding anticancer compounds and their mechanism of action. It is hoped that the present publication when brought out would be of great use as a standard text-cum-reference for teachers, students, and researchers of various disciplines such as biomedical sciences, pharmaceutical sciences, marine biology, and fisheries science; a valuable reference for libraries of colleges and universities; and as a guide for the pharmaceutical industries involved in the development of new marine-derived anticancer drugs.

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CHAPTER 1

Introduction

Abstract: This chapter deals with the approved drugs sourced from marine biota, the pathophysiology of cancer, the anticancer potential of marine organisms, the most promising marine biota-derived anticancer compounds for the different types of human and cancer, biogeography of marine invertebrate species yielding anti cancer compounds, major constraints in the development of anticancer drugs and the remedial measures.

Keywords: Approved marine drugs, Anticancer marine compounds, Cancer pathophysiology, Constraints in marine anticancer drug development, Human cancer types, Marine biota, Remedial measures.

INTRODUCTION

The total global biodiversity in terms of both prokaryotic and eukaryotic organisms has been estimated as 500×10^6 species and in the marine ecosystems, about 250,000 species have been described. These marine organisms produce secondary metabolites as their defense tools to resist predators and facilitate their survival in extreme environmental conditions such as variations in temperatures, salinity, pressure, *etc.* Such secondary metabolites of marine organisms have been reported to offer extraordinary chemical and pharmacological scope. While marine flora such as seaweeds and mangroves have been used for medicinal purposes worldwide since ancient times, marine invertebrate animals have attracted the attention of researchers only in the last 50 years. It is worthy of mention here that less than 5% of the deep sea has only been explored till now and less than 0.01% of the deep-sea floor has been sampled thoroughly [1].

Approved Drugs Sourced from Marine Biota

The marine environment has been reported to possess immeasurable chemical diversity and it is an extraordinary resource for therapeutically important chemicals. The unique structural scaffolds and biological modes of action of these

chemicals make them lead compounds in drug discovery. Research on the secondary metabolites of marine organisms began only in the 1950s with Bergmann and coworkers' discovery of spongothymidine and spongouridine derived from the Caribbean sponge *Tectitethya crypta.* The reports on the geographic origin of the marine compounds showed that Australia contributed almost a quarter (24%) of these compounds followed by the South China Sea (18%) and the Pacific Ocean (17%) [2].To date, more than 28,000 compounds derived from marine organisms have been reported and more than 1000 new marine-derived compounds have been discovered each year since 2008. Although the number of promising bioactive compounds from the marine biota is on the increase, the search for marine biota-derived drugs is relatively recent, and only in the middle part of the 20th century, the scientists began to systematically probe the seas and oceans for new drugs. Today, the pipeline process from the basic research of a bioactive molecule to the regulatory approval by the Food and Drug Administration (FDA) takes about 15 years and costs several million dollars. However, it is also worth of mentioning here that less than 12% of the potential drugs get final approval [3]. The stages and time estimates in the development and approval of a drug are given in Table **1**.

Table 1. Stages and Time Estimates in the Development and Approval of Drugs [3].

Stage	Estimated Time (Yrs)
Basic Research and Drug discovery	5
Preclinical Trials	1.5
Clinical Trials (Phase I,II & III)*	6
FDA Review	2
Large Scale Manufacturing	2

* Number of Volunteers: Phase I, Tens; Phase II, Hundreds; Phase III, Thousands.

Cancer as a Major Public Health Problem

Cancer has been reported to be a major public health problem worldwide and is the second leading cause of death in the United States. As per the report of the US National Cancer Institute, 21 million new cases may appear in the coming two decades. Africa, Asia, and Central and South America are considered to be the most vulnerable countries where 7 out of 10 deaths are due to malignant neoplasms termed as cancer. However, tumor and cancer are also interchangeably used occasionally. The deadliest cancers are believed to be lung cancer, breast cancer, prostate cancer, colon cancer, pancreatic cancer, liver cancer, ovarian cancer, leukemia, non-Hodgkin's lymphoma, and corpus and uterus cancer. Among the usual cancer treatment forms *viz.* surgery, radiotherapy, and

chemotherapy, the former two are primarily indicated for solid tumors and chemotherapy assumes greater significance as this systemic drug-based treatment is known to interfere with the process of growth and cell division in tumor cells. Further, this chemotherapy is currently undergoing a significant revolution due to the introduction of a very large number of new arsenal drugs and less side effects of such target-oriented drugs. However, these drugs have not yielded the desired results; and recurrence of tumor and onset of metastasis often occur with such therapies. Therefore, there is an urgent need to search for new compounds with greater therapeutic potency and fewer side effects. In this connection, the seas and oceans could play an important role with their huge pharmaceutical biodiversity in general and anticancer potential in particular.

Pathophysiology of Cancer

In the development of cancer in the human body, several stages are involved. A normal cell may get damaged by either endogenous genetic and biological factors or exogenous factors like human diet and body mutation. Such damaged cells may either attain apoptosis (cell death) or undergo uncontrolled cell division which leads to mass forming and finally neoplasia. The neoplasia is nothing but the uncontrolled, abnormal growth of cells which is termed a neoplasm or tumor. The tumor may be benign (gentle) or become malignant (cancer). Generally, a balance between proliferation and programmed cell death is maintained in the form of apoptosis under normal conditions by regulating both processes tightly. On the other hand, in carcinogenesis, normal cells are transformed into cancer cells.

Anticancer Potential of Marine Organisms

Owing to their diverse and highly complex habitats and lifestyle, the marine species represent a largely unexplored source of potential anticancer agents. The anticancer compounds are mainly derived from mollusk/cyanobacterium (blue-green algae) (64%), sponge (14%), tunicate(14%), bacterium (4%) and fungus (4%) in that order. It is also worthy of mention here that 7 marine biota-based drugs have so far been approved for marketing; 23 compounds are in clinical trials between phases I and III; and more than one thousand compounds are undergoing preclinical studies. Further, among those marine biota-derived drugs in clinical use, 4 drugs *viz.* cytarabine (Cytosar®), trabectedin (Yondelis®), eribulin mesylate (Halaven®) and the conjugated antibody brentuximab vedotin (Acentris®). are presently used in the treatment of cancer [4]. A total of about 560 anticancer compounds have so far been derived from marine organisms (invertebrates) and both sponges and cnidarians contribute to more than 85% as shown in Table **2**.

CHAPTER 2

Marine Bio-Chemical Diversity: Promising Anticancer Groups

Abstract: This chapter deals with marine biodiversity and its constituents possessing anticancer activity. The different potential groups of marine plants such as microalgae (*e.g.* cyanobacteria), macroalgae (seaweeds), seagrasses, and mangroves; marine invertebrates *viz.* sponges, cnidarians, bryozoans, molluscs, and echinoderms; and tunicates among chordates producing anticancer compounds have been identified. The chemical diversity of anticancer compounds representing different chemical classes *viz.* alkaloids, terpenes, peptides, polyketides, polyphenols, glycosides *etc.* is also dealt with.

Keywords: Anticancer marine biodiversity, Anticancer chemical diversity, Anticancer marine plants, Anticancer marine invertebrates.

INTRODUCTION

According to the World Register of Marine Species (WoRMS), the known marine species are about 240,000. Many of these species are influenced by environmental factors, such as temperature, pressure, pH, light, salinity, *etc.* which make them produce secondary metabolites for helping the species in their communication, defense/offense, or competition. Depending on their molecular targets and structural features, these compounds are known to share different anticancer activities. The therapeutic importance of marine biodiversity was made known only after the chemical investigation of the first marine organism *viz.* the Caribbean sponge (*Cryptotethya crypta*) [1]. Subsequently, the anticancer importance of marine organisms such as marine plants (microalgae such as diatoms, dinoflagellates, and cyanobacteria; macroalgae (seaweeds), seagrasses, and mangroves; and marine invertebrates (sponges, cnidarians, bryozoans, molluscs, and echinoderms); and tunicates has been reported.

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Promising Anticancer Marine Biodiversity

Marine Microalgae

Among the marine microalgae, certain species of green algae, blue-green algae (cyanobacteria), golden-brown, and yellow algae, yellow-green algae (diatoms), dinoflagellates, and red alga have been reported to possess anticancer compounds. Among these components, the cyanobacteria (blue-green algae) however, dominate with their larger number of anticancer species.

The peptide and polyketide metabolites of this microalgae have been reported to be effective for inducing apoptotic death of cancer cells or by affecting cell signaling *via* activation of the protein kinase c family. About 50% of the 41 screened strains of cyanobacteria have shown the ability to cause cancer cell death [1]. The anti-microtubule agents, *i.e.*, dolastatin 10 and curacin A of these cyanobacterial strains have been clinically evaluated for the treatment of cancer and these compounds are believed to serve as lead drug candidates for the synthesis of a number of analogs/derivatives. Recent research findings have shown that the under-exploited benthic cyanobacteria from temperate marine areas could be novel drug sources against leukemia. Further intensive investigations are therefore urgently needed on the potential anticancer activities and clinical uses of these marine cyanobacterial species.

Macroalgae (Seaweeds)

Marine macroalgae or seaweeds form an important component of marine ecosystems due to their large habitats, high biodiversity, and specific living conditions. They have long been considered as food and functional food due to their important bioactive elements including carotenoids, dietary fiber, protein, essential fatty acids, vitamins (A, B, B12, C, D, E), and minerals such as Ca, P, Na, and K [1]. These algae have also served as potential drug sources as they possess a vast number of major secondary metabolites such as terpenes, polyphenols, polysaccharides, phlorotannins, phycobiliproteins, carotenoids, and pigments. Among these chemical classes, the compounds of terpenes, polysaccharides, and polyphenols are of great interest for their antitumor activity. The anticancer compounds from these seaweeds have been reported to induce cancer cell death *via* various signaling pathways and mechanisms. Further, these compounds prevent resistance or tolerance of cancer cells. For example, the sulfated polysaccharide, fucoidan of the different species of seaweeds acts as an anticancer agent through various signaling pathways which include cell cycle arrest, apoptosis, and anti-angiogenesis by inhibiting vascular endothelial growth factor formation, and natural killer cell activation.

Mangrove Plants

Mangroves are halophytic (salt-tolerant) plants and they grow on brackish water coasts and intertidal seawater systems of the tropical and subtropical coastlines. The world mangroves occupy the major geographic regions *viz.* east area mangroves from the west and central Pacific to the southern end of Africa; west area covering the west coast of Africa and both east and west coasts of the Americas. These mangroves are considered to be one of the most ecologically and economically significant ecosystems due to their wide range of services which include, carbon storage and sequestration, enhancement of fisheries, and coastal protection against natural disasters. Further, these ecosystems, protect the nearby marine ecosystems and improve their quality through nutrient cycling and by neutralizing the pollutants originating from aquatic and terrestrial means. Furthermore, they support commercially important marine life and wildlife by providing them with habitat and food. Several species of mangroves are of great application value in various industrial sectors such as pharmaceutics, cosmetics, and materials. In recent decades, these plants have also attracted the attention of researchers due to their unique secondary metabolites with various bioactivities in general and anticancer activity in particular. For example, triterpenoid compounds xylogranatins A-D; and limonoids granaxylocapins A, B derived from the mangrove *Xylocarpus granatum* have been reported to possess cytotoxicity in various cancer cell lines including P-388 leukemia [8].

Marine Invertebrates

Marine Sponges

Marine sponges belong to the phylum Porifera with four classes: *viz.* Calcarea, Demospongiae, Hexactinellida, and Homoscleromorpha. The known and described species of this phylum are more than 9000. These sessile invertebrates represent the richest source of marine bioactive compounds. Of the 28,000 new compounds of marine origin identified so far, the sponges and their associated microorganisms contribute to about 30% with 5300 compounds. The chemical classes of these secondary metabolites include alkaloids, terpenes, amino acid derivatives, cyclic peptides, nucleosides, sterols, peroxides, fatty acids, *etc.* Among these compounds, about 60 of them have been reported to possess chemopreventive and/or anticancer potential [9]. The successful discovery and identification of spongothymidine and spongouridine from the Caribbean sponge *Tethya crypta* led to the development of a clinically anticancer agent *viz.* AraC (cytosine arabinoside); and Eribulin, a synthetic version of halichondrin B, produced by the sponge *Halichondria okadai* has shown potential activity against pretreated metastatic breast cancer cells [1]. The origin of the secondary

CHAPTER 3

Marine Biota-based Anticancer Drug Candidates in Pipeline

Abstract: This chapter deals with the approved and marketed anticancer drugs derived from marine sponges, mollusks/cyanobacteria, and tunicates; marine biota-derived anticancer compounds in clinical trials *i.e* in III, II, and I phases; and bioactive new chemical entities (NCEs) with anticancer function from marine biota. Limiting factors in the development and approval of drugs from marine biota and significant challenges in the development and approval of marine drugs are also given.

Keywords: Challenges in drug development, Clinical trials, Marine anticancer drugs, New chemical entities, Limiting factors.

INTRODUCTION

In recent decades, the hallmarks of cancer have been updated every now and then owing to its complexity. From 2010 onwards, several marine biota- derived drugs have been approved by the Food and Drug Administration (FDA) (USA) and other world regulatory authorities for the treatment of various types of cancer. Such marketed drugs include panobinostat and eribulin mesylate from marine sponges; plitidepsin, lurbinectedin and trabectedin from the tunicates; and brentuximab vedotin; polatuzumab vedotin; enfortumab vedotin; belantamab mafodotin; disitamab vedotin; and tisotumab vedotin from the marine mollusk-associated cyanobacteria. Based on their structural features and molecular targets, these compounds possess various modes of action in anticancer activities.

APPROVED AND MARKETED ANTICANCER DRUGS DERIVED FROM MARINE SPONGES

The marine bio-drug discovery started in the 1960s, and some bioactive compounds were approved. Among them, the oldest antileukemic compound *viz*, Cytarabine ARA-C was isolated in 1959 from the marine sponge *Tethya crypta* by Walwick at the University of California. Subsequently, two anticancer synthetic

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analogues–derivatives, developed from lead molecules of these sponges were approved [18] and they are discussed below:

Eribulin Mesylate (E7389, Halaven®)

The eribulin mesylate is the simplified synthetic analog of halichondrin B, which is a macrolide molecule derived from the marine sponge *Halichondria okadai* (Phylum: Porifera; Class: Demospongiae). Halichondrin B was found to show cytotoxic activity in murine models of solid tumors and leukemia. Due to the low yields of this compound from the above sponge species, the production of synthetic halichondrin B was necessitated, and subsequently, many analogs, like eribulin mesylate were developed. Eribulin is presently used for treating metastatic breast cancer. In 2010, it was approved in the USA by the FDA as Halaven® and by the European Medical Agency (EMA) in 2011 [18].

Panobinostat (LBH-589, Farydak®)

Panobinostat is a synthetic analog of Psammaplyn A, which was derived from the marine sponge, *Pseudoceratina purpurea* (Class: Demospongiae). After the discovery of this compound, many derivatives like psammaplyn B-D and biprasin and psammaplyn E–J were obtained [18].

The observed features of the approved compounds derived from the marine sponges are given in Table **1**.

Table 1. Approved compounds derived from the marine sponges [18].

Compound	Chemical Class	Source Species	Mode of Action
Eribulin mesylate	Macrolide	*Halichondria okadai*	Interfering tubulin polymerization
Panobinostat	Hydroxamic acid derivative	*Pseudoceratina purpurea*	Histone deacetylase (HDAC) inhibitor; Aminopeptidase-N and DNA Methyltransferase inhibitor

APPROVED AND MARKETED ANTICANCER DRUGS DERIVED FROM MARINE MOLLUSKS/CYANOBACTERIA ASSOCIATION

In recent years, several antibody-drug conjugates (ADCs) have been approved. Such ADCs were derived from the anticancer molecules produced by the symbiosis of cyanobacteria (blue-green algae) and molluscs. For the development of these anticancer drugs, the cyanobacterial species, *Symploca hynoides* and *Lyngbya majuscula*; and molluscan species *Dolabella auricularia* were the significant contributors [18]. The description of the approved and marketed

anticancer drugs derived from marine mollusks/cyanobacteria association [18**]** is given below.

Brentuximab Vedotin ((SGN-35, Adcetris®)

For this approved ADC, the linear pentapeptides dolastatins produced by the sea hare, *Dolabella auricularia* (Phylum: Mollusca; Class: Gastropoda) were the contributing compounds. However, the production of these compounds was subsequently found to be due to *Symploca hydnoides* and *Lyngbya majuscula* (Phylum: Cyanobacteria; Order: Oscillatoriales), the diet species of the mollusc.

Polatuzumab Vedotin

This is another approved ADC.

Enfortumab Vedotin-Eifv (Padcev®)

This FDA-approved drug treats metastatic or locally advanced urothelial cancer.

Disitamab Vedotin

This approved ADC has been reported to regulate cell duplication, proliferation and apoptosis. The antibody present in this molecule is believed to be used as a target for anticancer compounds.

Tisotumab Vedotin-tftv (Tivdak®)

It is a vedotin ADC associated with a specific antibody. It is for the treatment of cervical, ovarian and bladder cancers.

Belantamab Mafodotin-blmf (Blenrep®)

It is a recently approved drug by the FDA and European Medicines Agency (EMA) and is used for treating relapsed or refractory multiple myeloma.

The chemical class and mode of action of the approved anticancer drugs derived from the marine mollusks/cyanobacteria association are given in Table **2**.

Table 2. Approved anticancer drugs derived from the marine mollusks/cyanobacteria association [18].

Compound	Chemical Class	Source Species Mollusc/Cyanobacteria	Mode of Action
Brentuximab vedotin (Fig. **11**)	ADC (MMAE + CD30	*Dolabella auricularia / Symploca hynoides, Lyngbya majuscula*	Microtubulin targeting agent *via* CD 30

CHAPTER 4

Anticancer Potential of Marine Plants

Abstract: This chapter identifies the potential species of the various groups of marine plants such as microalgae (microscopic green algae, blue-green algae, golden-brown, and yellow algae, yellow-green algae and dinoflagellates and red alga), macroalgae or seaweeds *viz.* green algae, brown algae and red algae), seagrasses, mangrove plants, and halophytes; and their anticancer compounds with the mechanism of actions.

Keywords: Anticancer compounds, Halophytes, Microalgae, Macroalgae, Mangrove plants, Mechanism of action, Seaweeds, Seagrasses.

INTRODUCTION

Marine medicinal plants include microalgae, macroalgae (seaweeds), seagrasses, mangroves and halophytes. Among these, marine microalgae, seaweeds (macroalgae) and mangroves have been reported to possess significant pharmaceutical compounds of human health value. The microalgae such as cyanobacteria (blue-green algae), golden-brown and yellow algae, yellow-green algae (diatoms) and dinoflagellates are considered to be excellent sources of pigments, lipids, carotenoids, omega-3 fatty acids, polysaccharides, vitamins, *etc.*, and there is an increasing demand for their use as nutraceuticals and food supplements. Some microalgae such as cyanobacteria and dinoflagellates are known for their anti-cancer activity. The seaweeds (macroalgae) also have been reported to have several health-promoting natural products such as sulphated polysaccharides, polyphenolics, terpenoids, flavonoids, pigments, MUFAs (monounsaturated fatty acids), PUFAs (polyunsaturated fatty acids), and HUFAs (highly unsaturated fatty acids), essential amino acids, vitamins, and essential minerals. These compounds are believed to be of great use in the development of new pharmaceutical and nutraceutical products. While the bioactive compounds of these algae have several bioactivities including anti-tumor effects, their nutraceutical products are known to prevent human health problems like diabetes, cancer and cardiovascular diseases. Similarly, mangrove plants like *Rhizophora stylosa, Sonneratia paracaseolaris, Aegiceras corniculatum, Excoecaria agallocha, Bruguiera cylindrica, Ceriops taga,* and *Xylocarpus* spp. have been

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reported to possess potent anti-tumor compounds. In this chapter, the most promising species of marine plants, their anticancer compounds, and their modes of action are dealt with.

Microalgae

Green Algae

Chlorella ellipsoidea

The carotenoid extract of this species acted against HCT-116 (colon carcinoma) cell line and an IC50 value of 40 µg/mL was recorded [3].

Chlorella sorokiniana

At an active concentration of 0.0156 to 1 µg/mL, its water extract displayed inhibitory activity against lung adenocarcinoma (CL1-5), and the cell viability was reduced to 20% progressively [3].

***Chlorella* sp.**

The extracts of the species of *Chlorella viz. Chlorella spaerckii, Chlorella stigmatophora, Chlorella salina, Chlorella marina*, and *Chlorella ovalis,* which possess peptides have shown antiproliferative activity and cytotoxicity induced by ultraviolet B (UVB). Further, these compounds decreased cleaved PARP-1; prevented DNA damage and fragmentation; and reduced pFADD expression [23].

Dunaliella tertiolecta

A glycoglycerolipid compound, glycerol 1-(9Z, 12Z, 15Z-octadecatrienoate)-2-(4Z,7Z,10Z, 13Z-hexadecatetraenoate)-3-O-β-D-galactopyranoside (Fig. **1**) derived from this species displayed antimitotic activity against Melanoma A2058 cell line with 35 and 44% activity at 100 and 50 µg/mL concentrations, respectively [24]. (Martínez *et al.*, 2022). Andrade *et al.* (2018) reported that its carotenoid pigment *viz.* violaxanthin exhibited cytostatic activity against breast adenocarcinoma (MCF-7) at an active concentration of 40 µg/mL[3].

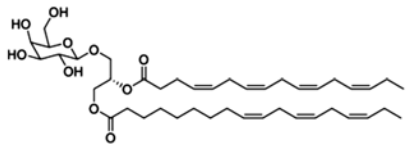

Fig. (1). Glycerol 1-(9Z,12Z,15Z-octadecatrienoate) 2-(4Z,7Z,10Z,13Z-hexadecatetraenoate)-3-O-β-D-galactopyranoside.

Tetraselmis suecica

The extracts of this species have shown rich α-tocopherol content and other vitamins and have shown cytotoxicity towards NCI-H460, MCF-7, HL-60, and tumor cells [25].

BLUE-GREEN ALGAE

Anabaena sp.

The extracts of *Anabaena* sp. M44, M30, and M27 strains triggered apoptosis and these extracts could serve as VGSC (Voltage-gated Na^+ channel) inhibiting drugs with activities against cancer migration, invasion, and proliferation [26].

Arthrospira platensis (= Spirulina platensis)

The polysaccharides isolated form this species showed antitumor activity [23]. Its phycocyanin possesses anti-cancer activities as shown in Table **1**.

Table 1. Anticancer activity of the pigment phycocyanin on human cancer cells [27].

Cell Line	Phycocyanin Conc.	IC50
HCT116	50ug/mL	18.8ug/mL
HeLa	80;120ug/mL	1104ug/mL
HepG2	100uM	13uM
A549	50ug/mL	99.2ug/mL
HT-29	50; 200ug/mL	-
MCF-7	5.66ug/mL	5.66ug/mL
A375	40uM	-

Calothrix sp.

Calothrixins A,B (Fig. **2**) of this species also showed promising anticancer activity against human HeLa cancer cells with IC50 values of 40 and 350 nM, respectively [28].

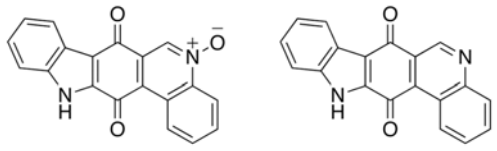

Fig. (2). Calothrixins A,B.

CHAPTER 5

Anticancer Potential of Marine Sponges

Abstract: This chapter deals with the anticancer activity of different chemical classes of compounds of marine sponges *viz.* alkaloids, terpenes, peptides and lipids. The mechanisms of action of the different compounds are also given.

Keywords: Anticancer compounds, Chemical classes of compounds, Marine sponges.

INTRODUCTION

Marine sponges (Phylum: Porifera), which are represented by about 15000 species are believed to be the oldest organisms surviving for more than 600 million years.

Among all marine organisms, these sponges are the richest source of marine bioactive compounds (ca. 5000) and are contributing to about 30% of all natural marine products identified so far. At least around 50 compounds of these sponges have the potential to be chemopreventive and/or anticancer agents.

The anticancer drug "Vidarabine" was first isolated by Bergmann and Feeney in the 1950s from a peculiar nucleoside isolated from a marine sponge, Tethya crypta. The chemical classes of these secondary metabolites such as sterols, alkaloids, terpenes, peptides, nucleosides, fatty acids, amino acid derivatives, and cyclic peptides are also well known for their cytotoxic, chemo-preventive and/or anticancer potential by different mechanisms, such as cell-cycle arrest, anti-inflammatory activity, apoptosis, *etc.* Considering the therapeutic importance of the marine sponge-derived bioactive metabolites,these organisms continue to be one of the most promising sources of new drug leads.

Anticancer Activity of Alkaloids of Marine Sponges

Aaptos aaptos

Compound(s) and their mode(s) of action: Its benzonaphthyridine alkaloid, isoaaptamine (Fig. **1**) exhibited potent cytotoxic activity against breast cancer T-47D cells. Further, this compound showed autophagy by allowing the orderly

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degradation (of unwanted components) and recycling of cellular components[137]. Furthermore, its compound aaptamine (Fig. **2**) aids in inducing apoptosis of NT2 and HepG2 cell lines at a dose of 1-50 uM and 50-100 uM, respectively [9]. Its four new aaptamine derivatives have also been reported to display significant cytotoxicity against HL60, K562, MCF-7, KB, HepG2, and HT-29 cells, with IC_{50} values in the range of 0.03 to 8.5 μM [138].

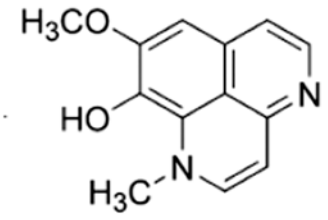

Fig. (1). Isoaaptamine.

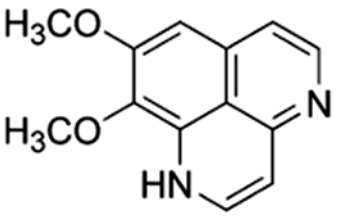

Fig. (2). Aaptamine.

Aaptos suberitoides

Compound(s) and their mode(s) of action: Among its bis-aaptamine alkaloids *viz.* suberitine A-D, suberitine B and D (Fig. **3**) displayed potent cytotoxicity against P388 cell lines, with IC(50) values of 1.8 and 3.5 μM, respectively [139]. Its aaptamine was found to induce apoptosis of MG63 and K562 cell lines at a dose of 30 μg/mL and 20–100 uM respectively [9].

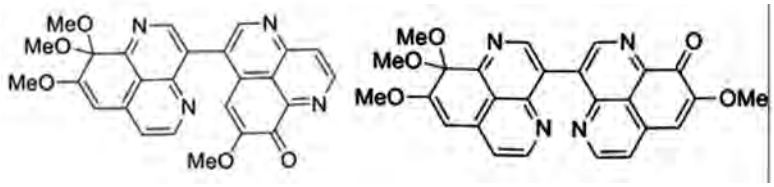

Fig. (3). Suberitine B, D.

Aaptos sp.

Compound(s) and their mode(s) of action: Its demethyl(oxy)aaptamine (Fig. **4**) and aaptamine induced apoptosis of THP-1 cell line at a concentration range of 10-25 uM[9]. Its demethyl(oxy)aaptamine (Fig. **4**) and aaptamines were found to induce apoptosis of the THP-1 cell line at a dose e of 10-25 uM [9]. Further, its isoaaptamine displayed anticancer activity against the P338 cancer cell line at an IC50 value of 0.28 ug/mL [140].

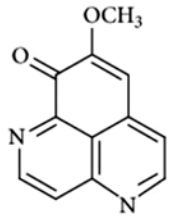

Fig. (4). Demethyl (oxy) aaptamine.

Aplysina aerophoba

Compound(s) and their mode(s) of action: The brominated alkaloid, isofistularin-3 (Fig. **5**) of this species induced apoptosis of Raji and U937 cell lines at a dose of 50 uM [9].

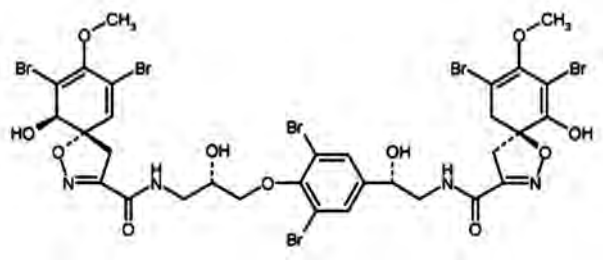

Fig. (5). Isofistularin-3.

Arenosclera brasiliensis

Compound(s) and their mode(s) of action: The tetracyclic alkylpiperidine alkaloids of this species *viz.* haliclonacyclamine E (Fig. **6**) and arenosclerin A- C (Figs. **7**-**9**) displayed cytotoxicity against HL-60, L929, B16, and U138 cancer cell lines [141].

CHAPTER 6

Anticancer Potential of Marine Cnidarians

Abstract: The anticancer potential of the marine organisms of the phylum: Cnidaria *viz.* medusae of Hydrozoa, Scyphozoa and Cubozoa; and soft, stony and black corals and sea anemones of Anthozoa are given in this chapter.

Keywords: Anthozoan soft corals, Anticancer potential, Cubozoan medusae, Hydrozoan medusae, Scyphozoan medusae, Stony and black corals, Sea anemones.

INTRODUCTION

Cnidarians are largely known to be largely responsible for the envenomations of humans during their fishing, and bathing in the marine environment, especially in tropical oceanic waters including Asia and Australia. Cnidarian stings are known to cause serious threats to human health by inducing local and systemic symptoms. However, these marine cnidarians have been reported to be a promising source of drug candidates in the development of new drugs or biomedical materials; for example, the vasoconstrictive compound and anaesthetic *viz.* palytoxin from the anthozoan species, *Palythoa toxica;* and prostaglandins (15R)-PGA2 derived from the gorgonian species *viz.Plaxaura homomalla* are well known. Further, in the recent decade, a considerable number of antioxidant and anticancer compounds have also been derived from these marine cnidarians and many of them are in clinical trials. This chapter deals with the anticancer compounds of the marine cnidarians species of and their venoms; and their mechanisms of action for pharmaceutical and therapeutic applications against various types of cancer.

Anticancer Compounds of Marine Hydrozoans (Phylum: Cnidaria; Class: Hydrozoa) and their Action Mechanisms

Abylopsis eschscholtzii

Its extract containing GFP-like proteins has been reported to emit bioluminescence, which is used in cancer therapy [172].

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Aeginura Grimaldi, Aegina citrea, Colobonema sericeum and Arctapodema sp.

The extracts of these species possess polypeptides which displayed cytotoxicity against mouse leukemia L1210 cells with IC50 values of 100,170,190 and 420 mg/ml, respectively [173,174].

Aequorea aequorea

The nematocyst extract of these species has shown cytotoxicity at an IC50 of 76.6 × 103 nematocysts/mL. Further, this extract has been reported to slow down the growth of cancer cells [174].

Chlorohydra viridissima

The extracts of this species produced toxicity in the human HEK293 (embryonic kidney) cell line [174].

Crossota rufobrunnea

The extract of this species possessing polypeptides displayed hemolytic effects at IC50 of 100mg/ml [173].

Halecium muricatum and Halecium beanie

These species have been reported to yield Swiss lipids *viz.* 1-Tetradecyl-sn-glycero- 3-phosphocholine and 1-O- hexadecyl-sn- glycero-3- phosphocholine. (Figs. **1**-**2**). While the former compound displayed activity against the lung fibroblast cell line, the latter displayed anticancer effects against the human MCF-7 (breast carcinoma) cell line at a concentration of 100 μg/ mL) [175].

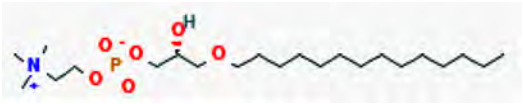

Fig. (1). 1-Tetradecyl -sn-glycero- 3-phosphocholine.

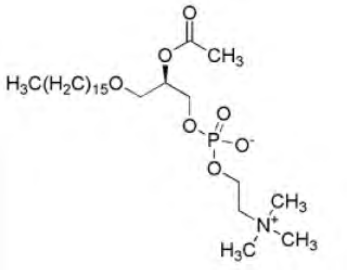

Fig. (2). 1-O- hexadecyl-sn- glycero-3- phosphocholine.

Halicreas minimum and Pantachogon Haeckel

The extracts of these species containing polypeptides displayed cytotoxicity against mouse leukemia L1210 cells with IC50 values of 750 and 160mg/ml, respectively [173,174].

Macrorhynchia philippina

This species has yielded pyrroloiminoquinones *viz.* macrophilone A- G . Of these compounds, macrophilone A, C (Figs. **3-4**) displayed potent and specific cytotoxic activity in the NCI 60 cancer cell line panel. Further, compound macrophilone A exhibited sub-micromolar cytotoxicity towards lung adenocarcinoma cells [5, 176].

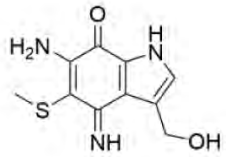

Fig. (3). Macrophilone A.

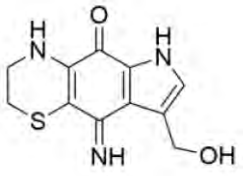

Fig. (4). Macrophilone C.

Physalia physalis

The two promising toxins *viz.* PpV9.4 and PpV19.3 purified from this siphonophore have been reported to show cytotoxicity [174].

Thuiaria breitfussi

The indole-oxazole-pyrrole alkaloids, breitfussin C-D (Figs. **5-6**) of this arctic hydrozoan species have been reported to possess cytotoxicity against several human cancer cell lines with IC50 values below 10 μM [5].

CHAPTER 7

Anticancer Potential of Marine Bryozoans

Abstract: This chapter deals with the anticancer and cytotoxic compounds of marine bryozoans and their mechanisms of action. Most of the anticancer compounds of these bryozoans were found to belong to the chemical classes alkaloids and lactones.

Keywords: Alkaloids, Anti cancer compounds, Cytotoxic compounds, Lactones, Marine bryozoans.

INTRODUCTION

The phylum Bryozoa includes filter-feeding, benthic invertebrates like moss animals, sea mats, or lace corals, which are found to be distributed in diverse marine habitats from the intertidal coastal areas to the deep sea. Most of the species of this phylum are colonial and are in different shapes like encrusting sheets to branched chains. These marine bryozoans are known to produce therapeutically important secondary metabolites of different chemical classes with various biological activities. The well known promising anticancer compound *viz.* bryostatin-1 derived from the marine bryozoan species *viz. Bugula neritina* was under investigation in Phase I/II clinical trials. However, the FDA (USA) has granted only orphan drug status to this compound in amalgamation with paclitaxel (a chemotherapy medication) for esophageal cancer as it has displayed minimal anti-tumor activity as a single agent. It is also worth mentioning here that only a total of about 250 new bioactive compounds have so far been derived and characterized from about 50 species of bryozoans although the number of marine bryozoan species is believed to exceed 8000. This is largely due to their taxonomic problems as most of them resemble seaweeds or members of other phyla like anthozoa or endoprocata. Another major constraint is the adequate supply of bioactive compounds from this organism as only a small amount of compounds are invariably collected from the collected larger quantities of species biomass. For example, it has been estimated that 13 tons of the marine bryozoan species *viz. Bugula neritina* needs to be harvested to obtain only 18 g of pure

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bryostatin I. Further, collection problems do exist as about 50% of the marine bryozoan species have habitats deeper than 40 m, and about 30% of the species are found to be distributed below 700 m in depth [12].

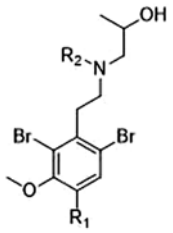
Anticancer and Cytotoxic Metabolites of Marine Bryozoans

Marine bryozoan species are known to have alkaloids which are believed to be the most common and promising class of bioactive compounds used in the development of anticancer drugs. The anticancer and cytotoxic effects of marine bryozoan species possessing alkaloid compounds are given below [12].

Anticancer Alkaloid Compounds of Marine Bryozoans

Amathia convoluta

The alkaloid compounds *viz.*, convolutamide A–F derived from this species, convolutamide A, B have been reported to display cytotoxic effects against human KB (epidermoid carcinoma) cell line and murine leukemia (L-1210) cells at IC50s of 2.8 and 4.8μg/mL, respectively . Furthermore, oxindole alkaloid compounds *viz.* convolutamydine A–D; and β-phenylethylamine alkaloid compounds namely convolutamine A–G (Figs. **1-7**) and lutamide A, C have also been isolated from this species. Among the convolutamydines, convolutamydine A displayed potent activity against human HL-60 (plomyelocytic leukemia) cells at doses of 0.1–25 μg/mL . Among the convolutamines, convolutamine A, C, and F showed inhibitory activity against adriamycin -resistant ADM/ P-388 with IC50s of 7,3, and 9.5 μg/mL; and against vincristine -resistant VCR/P-388 with IC50s of 3, 1.4, and 8 μg/mL, respectively.Moreover, its convolutamine B and D exhibited antimitotic activity against P-388 with IC50s of 4.8 and 8.6 μg/mL respectively; and convolutamine F acted against vincristine-resistant VJ300/ KB cell lines at an IC50 of 9.6 μg/mL. Furthermore, its lutamide A and C showed inhibitory activity against VJ300/KB cells with IC50s of 7.5 and 6.5 μg/mL respectively; and lutamide C acted against VCR/P-388 with an IC50 value of 4.8 μg/mL.



Figs. (1-3). Convolutamine A-C.

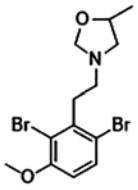


Fig. (4). Convolutamine D.

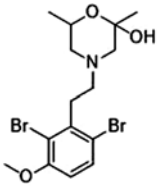
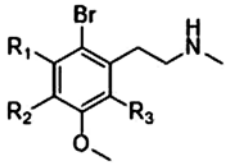


Fig. (5). Convolutamine E.

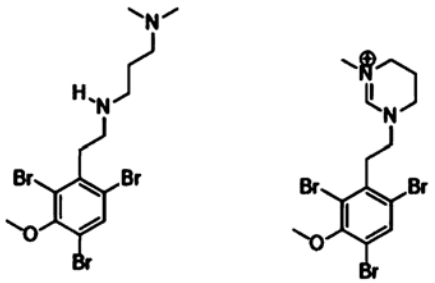
Convolutamine: R1=Br. R2=CH3; Convolutamine B: R1= H. R2= CH3; Convolutamine C; R1=Br. R2=H.



Figs. (6-7). Convolutamine F,G. (Convolutamine F: R1=H. R2=R3=Br; Convolutamine G: R1=R2=H. R3=Br.).

Amathia tortuosa

The alkaloids, convolutamines I–J (Figs. **8**, **9**) derived from this species exhibited potent activity against ATP competitive inhibitors.



Figs. (8-9). Convolutamines I–J.

CHAPTER 8

Anticancer Potential of Marine Shellfish

Abstract: This topic describes the anticancer metabolites of the components of marine shellfish such as crustaceasn (shrimp, lobsters, crayfish, and crabs), marine molluscs *viz.* bivalves (clams, oysters, *etc*), gastropods (snails, slugs, *etc.*) and cephalopods (squids, octopuses, and cuttlefish). Among the bioactive compounds of marine molluscs, the anti-proliferative and cytotoxic compounds accounted for 12 and 36%. Among echinoderms, the asteroids (starfish), echinoids (sea urchins) and holothuroids (sea cucumbers) are found to be pharmaceutically important. Among the bioactive metabolites of echinoderms, the cytotoxic or anti-proliferative metabolites accounted for 38%.

Keywords: Cephalopod ink, Echinoderms, Marine shellfish, Marine crustaceans, Marine molluscs.

INTRODUCTION

The fisheries term “shellfish” includes exoskeleton-bearing marine invertebrates such as the fauna of molluscs, crustaceans, and echinoderms. Marine crustaceans include members of shrimp, lobsters, crayfish, and crabs; marine molluscs have their representatives from bivalves (clams, oysters, *etc*), gastropods (snails, slugs, *etc.*) and cephalopods (squids, octopuses, and cuttlefish). Among the marine shellfish, the gastropods and echinoderms have been reported to possess rich anticancer compounds. The ink of cephalopods which are highly advanced and organized molluscs possesses many health benefits and as a traditional medicine in China, Greece and Rome. This cephalopod ink offers vast scope to develop new drugs. Among bivalves and gastropods, only a very small number of species have been examined for their bioactive compounds. A total of 255 new bioactive metabolites have been described from the marine molluscan fauna between 2010 and 2019 and the cytotoxic and anti-proliferative compounds have been reported to account for 36% and 12% respectively. Furthermore, the peptides, sterols terpenes, and polyketides were found to be 31, 8, 24, and 15% respectively; and other chemical classes including polyphenols were found to be 22% of the compounds. The echinoderm fauna, which are found only in the marine

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environments, constitute about 7000 species and inhabit the benthic ocean floors in their adult stages. The different groups of the phylum Echinodermata are sea stars and starfish (Class: Asteroidea); brittle stars (Class: Ophiuroidea); sea urchins (Class: Echinoidea); and sea cucumbers (Class: Holothuroidea). These echinoderms have been reported to produce largely glycosylated compounds including steroids, glycolipids and saponins. Among echinoderms, the members of Asteroidea, Echinoidea and Holothuroidea are known to produce promising anti-tumor compounds, which amount to 38%. Starfish-derived compounds include mainly asterosaponins and polyhydroxy steroid glycosides with promising anticancer, anti-inflammatory agents, neuritogenic, and antimicrobial properties. Sea urchins are known for their antimicrobial compounds such as peptides including short cationic peptides with positively-charged amino acid residues like strongylocins, centrocin 1 and 2 or their analogues and paracentrin 1. Further, sea urchin pigments, which are found in their test spines, coelomocytes or gonads yield powerful antioxidant compounds. The body wall of sea cucumbers contains mainly polysaccharides and collagen, which are known to display anticancer, anti-hypertensive, anti-angiogenic, anti-inflammatory, anti-diabetic, anticoagulation, antimicrobial, antioxidant, and anti-osteoclastogenic properties. Further, these animals contain saponins, cerebrosides and gangliosides with numerous biological activities. Overall, this phylum exhibits a great variety of bioactive compounds *viz.* cytotoxic or anti-proliferative (38%); anticoagulant (16%); antimicrobial (9%), and antioxidant (7%) [5, 183].

MARINE CRUSTACEANS

Shrimps

Litopenaeus vannamei

The peptides of this species have been reported to induce apoptosis and anticancer activities in the HCT-116 colon cancer cell line. There was an increased apoptosis rate of cells treated with the gradual and mix peptides of this species with percentage values of 75.5% and 76%, respectively [184].

Penaeus indicus

This Indian white shrimp exhibited anticancer activity against H460 and HEP-2 (human lung and liver cancer) cell lines [185].

Lobster and Shrimp Shell Wastes

The peptide fractions of the lobster and shrimp wastes have been reported to significantly inhibit the growth of both colon and liver cancer cells by 60% [186].

Marine Crabs

Calappa calappa

The hemolymph of this species has shown high anticancer activity on Vero cells. About Fifty percent (50%) IC50 of cytotoxicity was observed at the concentrations of 75, 100, 95, 100 and 95 µg mLG1 in MCF-7, HepG2, A549, Rhabdomyosarcoma, and HT-29 cell lines, respectively [187].

Chionoecetes opilio

At a pH of 6 and concentration of 188 g/mL, the KCl2 run 1 fraction of this species showed a mortality of 83.9%, 86.9%, 57%, and 93.2% for A549, BT549, HCT15, and PC3 cells, respectively. Further, at a concentration of 190 g/mL, its KCl2 run 2 fractions, exhibited mortality on A549 and PC3 cancerous cell lines with percentage values of 74% and 100% respectively [188].

Portunus segnis

Its extracts exhibited antimitotic effects against human HT-29 (colorectal adenocarcinoma) cell line. The IC50 values recorded for the aqueous extracts were found to be 44.33, 31.97, and 19.38 ug/mL during 24,48 and 72 hrs respectively; the corresponding values for the hexane extracts were 35.27, 25.07 and 19.25 ug/mL; 26.63, 15.13, and 10.12 ug/mL for the butanol extracts; and for ethyl acetate 48.14, 34.63 and 22.86 ug/mL respectively [19].

Serratia marcescens

The microbial pigment prodigiosin of the wastes of this animal has shown anti-tumor property by inducing apoptosis in human cervical carcinoma cancer (HeLa) cell lines in a dose-dependent manner with an iC50 range of 680-700nM [189].

Chitosan Derived from Crab Shell Wastes

The chitosan (Fig. **1**) derived from the crab shell wastes has been reported to show anticancer effects. The chitosan-based nanoparticles conjugated with glutaraldehyde (ChNP-GA) were found to significantly reduce the viability of HCT-116 cancer cells in a dose-dependent manner besides reducing the cell morphology of the cancer cells (nuclear condensation and nuclear augmentation) of the cancer cells. Further, the combined treatment of chitosan-based hydrogel and cancer drug, PTX decreased the viability of SKOV3, one of the human ovarian tumor cell lines, by 3.33 fold, Furthermore, the glycyrrhetinic acid-modified chitosan (GACTS)-based 5-FU (anti-cancer drug 5-fluorouracil) nanoparticle showed inhibitory activity on SMMC-7721 and SW480 cell lines and

CHAPTER 9

Anticancer Potential of Marine Chordates

Abstract: The anticancer compounds of tunicates and marine fishes *viz.* elasmobranchs and teleosts are dealt with in this chapter.

Keywords: Anticancer compounds, Elasmobranchs, Tunicates, Teleosts.

INTRODUCTION

Tunicates (Subphylum: Tunicata) are the marine invertebrate chordates and they earn the common name due to the presence of a cellulose compound *viz.* tunicin in their external layer of the body. Members of tunicates are benthic and sessile (Ascidiacea) or pelagic (Thaliacea or Larvacea). Among the tunicates, the ascidians or sea squirts which constitute more than 2300 species of the total tunicates species numbering about 3000. The bioactive compounds of tunicates are represented by alkaloids, (50%) polyketides (37%) and peptides (13%). Among the members of tunicates, the ascidians have been reported to possess promising anticancer compounds, which amount to 58% of their total bioactive metabolites. It is worthy of mention here that three of the anticancer compounds of these ascidians have already entered the clinical trials [5]. Among the marine fishes, the protein hydrolysates of certain species are a promising source of active biopeptides, which possess anticancer activity on several cell lines. The small protein syngnathids derived from the whole body of Syngnathus arcus was found to possess anticancer activity of human lung adenocarcinoma (A-549) and lymphoblastic leukaemia (CCRF-CEM) cell lines [220].

Tunicates

The anticancer compounds of marine ascidians (Tunicates; Ascidiacea) and their mechanisms of action are given below [221].

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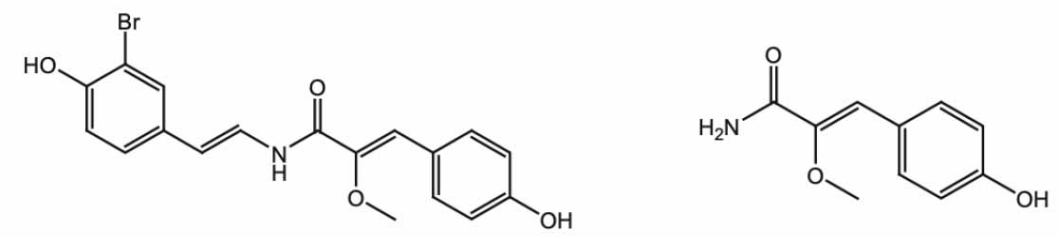
Aplidium altarium

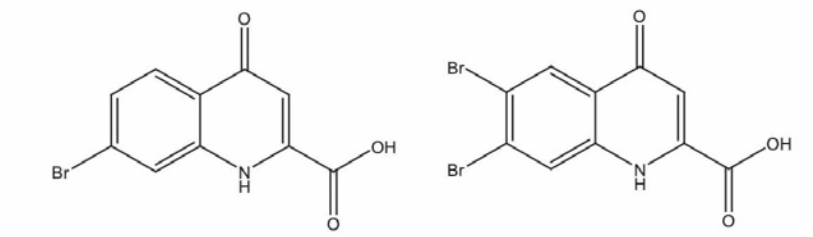
The tyrosine derivatives, botryllamides K, L (Figs. **1-2**) isolated from this species exhibited weak cytotoxicity against MCF-7 breast cancer cell line with IC50 values of 74, and 91 µM respectively; and against H460-lung cancer cell line with I C50s of 91 and 89 µM, respectively.



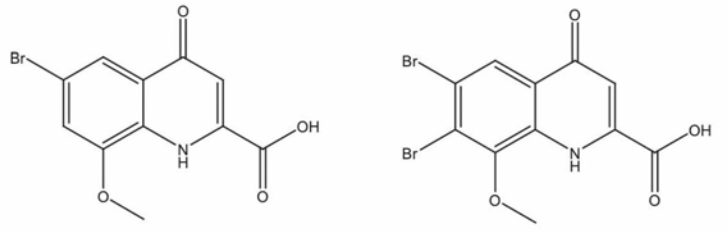
Figs. (1-2). Botryllamides K, L.

Aplidium caelestis

The quinoline carboxylic acids *viz.* caelestines A–D (Figs. **3-6**) of this species exhibited weak cytotoxicity against MCF-7 breast adenocarcinoma cancer cells with IC50s of 39, 49, 40, and 38 µM respectively; NFF (neonatal foreskin fibroblasts) with 57, 66, 58, and 68 µM respectively ; and against MM96L melanoma cell line with 62, 69, 54, and 52 µM; respectively.



Figs. (3-4). Caelestine A,B.

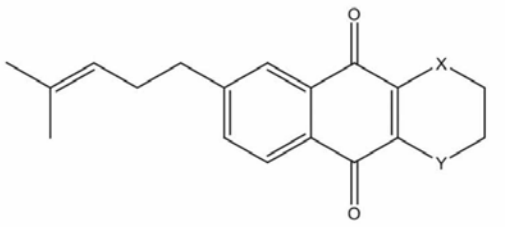


Figs. (5-6). Caelestine C,D.

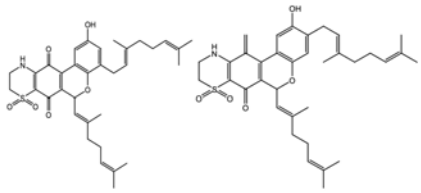
Aplidium conicum

The alkane derivatives, conicaquinone A,B (Figs. **7**-**8**) of this species showed significant cytotoxic activity against C6 (rat glioma) cells with IC50s of 2.1 and 5 μg/mL respectively.

Furthermore, the prenylated benzoquinones, thiaplidiaquinone A, B (Figs. **9**-**10**) displayed potent cytotoxicity against human leukemia T Jurkat cells with an IC50 value of 3 μM. Furthermore, the synthetic analogue aplidinone A Fig. (**11**) of this species reported cytotoxicity and pro-apoptotic activity against kidney cancer 293T and human lung adenocarcinoma A549 cell lines with IC50 values of 8.7 and 13 μM, respectively. Aplidinone A has also been reported to potentially inhibit the activation of NF-κB (nuclear factor) pathway in human T-cell acute lymphoblastic leukemia cell line. It has also been reported that its meroterpenes *viz.* conithiaquinone A,B (Figs. **12**-**13**) displayed significant effects on the growth and viability of cells and conithiaquinone A exhibited moderate cytotoxic activity on human breast cancer cell line with an IC50 value of 44.5 μM.



Figs. (7-8). Conicaquinone : X= SO2, Y=NH.
Fig. (**8**). Conicaquinone: X= NH, Y=SO2.



Figs. (9-10). Thiaplidiaquinone A, B.

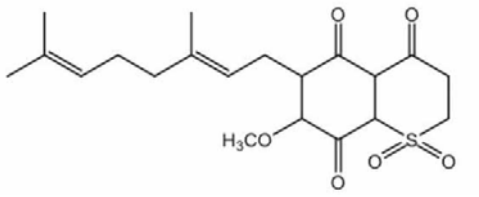


Fig. (11). Aplidinone A.

REFERENCES

[1] Khalifa SAM, Elias N, Farag MA, *et al.* Marine Natural Products: A Source of Novel Anticancer Drugs. Mar Drugs 2019; 17(9): 491.
[http://dx.doi.org/ 10.3390/md17090491] [PMID: 31443597]

[2] Barreca M, Spanò V, Montalbano A, *et al.* Marine Anticancer Agents: An Overview with a Particular Focus on Their Chemical Classes. Mar Drugs 2020; 18(12): 619.
[http://dx.doi.org/ 10.3390 /md18120619] [PMID: 33291602]

[3] Martínez Andrade K, Lauritano C, Romano G, Ianora A. Marine Microalgae with Anti-Cancer Properties. Mar Drugs 2018; 16(5): 165.
[http://dx.doi.org/ 10.3390/md16050165] [PMID: 29762545]

[4] Zuo W, Kwok HF. Development of Marine-Derived Compounds for Cancer Therapy 2021.https://pubmed.ncbi.nlm.nih.gov/34203870/
[http://dx.doi.org/ 10.3390/md19060342]

[5] Romano G, Almeida M, Varela Coelho A, *et al.* Biomaterials and Bioactive Natural Products from Marine Invertebrates: From Basic Research to Innovative Applications. Mar Drugs 2022; 20(4): 219.
[http://dx.doi.org/ 10.3390/md20040219] [PMID: 35447892]

[6] Karthikeyan A, Joseph A, Nair BG. Promising bioactive compounds from the marine environment and their potential effects on various diseases. J Genet Eng Biotechnol 2022; 20(1): 14.
[http://dx.doi.org/ 10.1186/s43141-021-00290-4] [PMID: 35080679]

[7] Dayanidhi DL. + 13. Exploring the Diversity of the Marine Environment for New Anti-cancer Compounds. Front Mar Sci 2021; 7https://www.frontiersin.org /articles/10.3389 /fmars.2020. 614766/full

[8] Das G, Gouda S, Mohanta YK, Patra JK. Mangrove plants : A potential source of drugs. Indian J Mar GeoSci 2015; 44(5): 666-72.http://www.niscair.res.in /jinfo /ijms/ijms -forthcoming- articles/BKP-IJMS-PR-May %202015/MS%202501 %20Edited.pdf

[9] Calcabrini C, Catanzaro E, Bishayee A, Turrini E, Fimognari C. Marine Sponge Natural Products with Anticancer Potential: An Updated Review. Mar Drugs 2017; 15(10): 310.
[http://dx.doi.org/ 10.3390/md15100310] [PMID: 29027954]

[10] Rocha J, Peixe L. Cnidarians as a source of new marine bioactive compounds- -an overview of the last decade and future steps for bioprospecting. Mar Drugs 2011; 9(10): 1860-86.https://pubmed.ncbi. nlm.nih. gov/22073000/ [PMID: 22073000]

[11] Oliveira CS, Caldeira CAS, Diniz-Sousa R, *et al.* Pharmacological characterization of cnidarian extracts from the Caribbean Sea: evaluation of anti-snake venom and antitumor properties. J Venom Anim Toxins Incl Trop Dis 2018; 24(1): 22.
[http://dx.doi.org/10.1186/s40409-018-0161-z] [PMID: 30181737]

[12] Figuerola B, Avila C. The Phylum Bryozoa as a Promising Source of Anticancer Drugs. Mar Drugs 2019; 17(8): 477.
[http://dx.doi.org/10.3390/md17080477] [PMID: 31426556]

[13] Sima P, Vetvicka V. Bioactive substances with anti-neoplastic efficacy from marine invertebrates: Bryozoa, Mollusca, Echinodermata and Urochordata. World J Clin Oncol 2011; 2(11): 362-6.
[http://dx.doi.org/10.5306/wjco.v2.i11.362] [PMID: 22087434]

[14] Patil P, Sahu BK, Panigrahy RC. Marine Molluscs as a Potential Drug Cabinet: An Overview. Indian J Geo-Mar Sci 2015; 44(7): 461-70. [https://nopr.niscpr.res.in /bitstream/ 123456789/ 34841/1/IJMS%2044 (7)%20961- 970.pdf].

[15] Santhanam R, Ramesh S. Biology and Ecology of Pharmaceutical Marine Tunicates, (Series: Biology and Ecology of Pharmaceutical Marine Life) CRC Press. USA: Taylor & Francis 2019. [http://dx.doi.org/10.1201/9780429321788]

[16] Erwin PM, López-Legentil S, Schuhmann PW. The pharmaceutical value of marine biodiversity for anti-cancer drug discovery. Ecol Econ 2010; 70(2): 445-51. [http://dx.doi.org/10.1016/j. ecolecon.2010.09. 030]

[17] Saeed AFUH, Su J, Ouyang S. Marine-derived drugs: Recent advances in cancer therapy and immune signaling. Biomed Pharmacother 2021; 134. https://pubmed.ncbi.nlm.nih.gov/33341044/ [PMID: 33341044]

[18] Santaniello G, Nebbioso A, Altucci L, Conte M. Recent Advancement in Anticancer Compounds from Marine Organisms: Approval, Use and Bioinformatic Approaches to Predict New Targets. Mar Drugs 2022; 21(1): 24. [http://dx.doi.org/10.3390/md21010024] [PMID: 36662197]

[19] Han N, Li J, Li X. Natural Marine Products: Anti-Colorectal Cancer *In Vitro* and *In Vivo*. Mar Drugs 2022; 20(6): 349. [http://dx.doi.org/10.3390/md20060349] [PMID: 35736152]

[20] Dyshlovoy SA, Honecker F. Marine Compounds and Cancer: Updates 2022. Mar Drugs 2022; 20(12): 759. [http://dx.doi.org/10.3390/md20120759] [PMID: 36547906]

[21] Pelay-Gimeno M, García-Ramos Y, Jesús Martin M, *et al.* The first total synthesis of the cyclodepsipeptide pipecolidepsin A. Nat Commun 2013; 4(1): 2352. [http://dx.doi.org/10.1038/ncomms3352] [PMID: 23989475]

[22] Martín MJ, Rodríguez-Acebes R, García-Ramos Y, *et al.* Stellatolides, a new cyclodepsipeptide family from the sponge *Ecionemia acervus*: isolation, solid-phase total synthesis, and full structural assignment of stellatolide A. J Am Chem Soc 2014; 136(18): 6754-62. [http://dx.doi.org/10.1021/ja502744a] [PMID: 24725163]

[23] Wu J, Gu X, Yang D, *et al.* Bioactive substances and potentiality of marine microalgae. Food Sci Nutr 2021; 9(9): 5279-92. [http://dx.doi.org/10.1002/fsn3.2471] [PMID: 34532034]

[24] Martínez KA, Saide A, Crespo G, *et al.* Promising Antiproliferative Compound From the Green Microalga *Dunaliella tertiolecta* Against Human Cancer Cells. Front Mar Sci 2022; 9: 778108.https://www.researchgate.net/publication/35867473 [http://dx.doi.org/10.3389/fmars.2022.778108]

[25] https://en.wikipedia.org/wiki/Tetraselmis_suecica

[26] Pradhan B, Ki JS. Phytoplankton Toxins and Their Potential Therapeutic Applications: A Journey toward the Quest for Potent Pharmaceuticals. Mar Drugs 2022; 20(4): 271. [http://dx.doi.org/10.3390/md20040271] [PMID: 35447944]

[27] Braune S, Krüger-Genge A, Kammerer S, Jung F, Küpper JH. Phycocyanin from *Arthrospira platensis* as Potential Anti-Cancer Drug: Review of *In Vitro* and *In Vivo* Studies. Life (Basel) 2021; 11(2): 91. [http://dx.doi.org/10.3390/life11020091] [PMID: 33513794]

[28] https://accedacris.ulpgc.es/bitstream/10553/74363/2/0767079_00000_0000.pdf

[29] Keller L. + 12. Tutuilamides A-C: Vinyl-Chloride Containing Cyclodepsipeptides from Two Marine Cyanobacteria *Schizothrix* sp. and *Coleofasciculus* sp. with Potent Elastase Inhibitory Properties. ACS Chem Biol 2020; 15(3): 751-7. [http://dx.doi.org/10.1021/acschembio.9b00992] [PMID: 31935054]

[30] Leão PN, Costa M, Ramos V, *et al.* Antitumor activity of hierridin B, a cyanobacterial secondary metabolite found in both filamentous and unicellular marine strains. PLoS One 2013; 8(7): e69562.

[http://dx.doi.org/10.1371/journal.pone.0069562] [PMID: 23922738]

[31] Khalifa SAM, Shedid ES, Saied EM, *et al.* Cyanobacteria—From the Oceans to the Potential Biotechnological and Biomedical Applications. Mar Drugs 2021; 19(5): 241.
[http://dx.doi.org/10.3390/md19050241] [PMID: 33923369]

[32] Costa M, Garcia M, Costa-Rodrigues J, *et al.* Exploring bioactive properties of marine cyanobacteria isolated from the Portuguese coast: high potential as a source of anticancer compounds. Mar Drugs 2013; 12(1): 98-114.
[http://dx.doi.org/10.3390/md12010098] [PMID: 24384871]

[33] Kurisawa N, Iwasaki A, Jeelani G, Nozaki T, Suenaga K, Iheyamides A-C. Iheyamides A–C, Antitrypanosomal Linear Peptides Isolated from a Marine *Dapis* sp. Cyanobacterium. J Nat Prod 2020; 83(5): 1684-90.
[http://dx.doi.org/10.1021/acs.jnatprod.0c00250] [PMID: 32352773]

[34] https://accedacris.ulpgc.es/bitstream/10553/74363/2/0767079_00000_0000.pdf

[35] Konstantinou D, Voultsiadou E, Panteris E, Zervou SK, Hiskia A, Gkelis S. *Leptothoe*, a new genus of marine cyanobacteria (Synechococcales) and three new species associated with sponges from the Aegean Sea. J Phycol 2019; 55(4): 882-97.
[http://dx.doi.org/10.1111/jpy.12866] [PMID: 31001838]

[36] Liu L, Rein KS. New peptides isolated from Lyngbya species: a review. Mar Drugs 2010; 8(6): 1817-37.
[http://dx.doi.org/10.3390/md8061817] [PMID: 20631872]

[37] Gunasekera SP, Ritson-Williams R, Paul VJ. Carriebowmide, a new cyclodepsipeptide from the marine cyanobacterium *Lyngbya polychroa*. J Nat Prod 2008; 71(12): 2060-3.
[http://dx.doi.org/10.1021/np800453t] [PMID: 19007282]

[38] Thornburg CC, Thimmaiah M, Shaala LA, *et al.* Cyclic depsipeptides, grassypeptolides D and E and Ibu-epidemethoxylyngbyastatin 3, from a Red Sea *Leptolyngbya* cyanobacterium. J Nat Prod 2011; 74(8): 1677-85.
[http://dx.doi.org/10.1021/np200270d] [PMID: 21806012]

[39] Tang HF, Yi Y-H, Yao XS, Xu QZ, Zhang SY, Lin HW. Bioactive steroids from the brown Alga *Sargassum carpophyllum*. J Asian Nat Prod Res 2002; 4(2): 95-101.
[http://dx.doi.org/10.1080/10286020290027362] [PMID: 12067165]

[40] https://accedacris.ulpgc.es/bitstream/10553/74363/2/0767079_00000_0000.pdf

[41] Thornburg CC, Cowley ES, Sikorska J, *et al.* Apratoxin H and apratoxin A sulfoxide from the Red Sea cyanobacterium *Moorea producens*. J Nat Prod 2013; 76(9): 1781-8.
[http://dx.doi.org/10.1021/np4004992] [PMID: 24016099]

[42] Sousa ML, Preto M, Vasconcelos V, Linder S, Urbatzka R. Antiproliferative Effects of the Natural Oxadiazine Nocuolin A Are Associated With Impairment of Mitochondrial Oxidative Phosphorylation. Front Oncol 2019; 9: 224.
[http://dx.doi.org/10.3389/fonc.2019.00224] [PMID: 31001482]

[43] Li Z, Guo M. Healthy efficacy of *Nostoc commune* Vaucher. Oncotarget 2018; 9(18): 14669-79.
[http://dx.doi.org/10.18632/oncotarget.23620] [PMID: 29581873]

[44] Wali AF, Majid S, Rasool S, *et al.* Natural products against cancer: Review on phytochemicals from marine sources in preventing cancer. Saudi Pharm J 2019; 27(6): 767-77.
[http://dx.doi.org/10.1016/j.jsps.2019.04.013] [PMID: 31516319]

[45] Martins J, Campos A, Leão PN, Vasconcelos V. Investigation of HDAC and 20S Proteasome Inhibitors from Cyanobacteria p.117. Mar Drugs 2020; 18. [Synopsis].

[46] Sumimoto S, Kobayashi M, Sato R, *et al.* Minnamide A, a Linear Lipopeptide from the Marine Cyanobacterium *Okeania hirsuta*. Org Lett 2019; 21(4): 1187-90.

[http://dx.doi.org/10.1021/acs.orglett.9b00135] [PMID: 30730753]

[47] Nweze JA, Mbaoji FN, Huang G, *et al.* Antibiotics Development and the Potentials of Marine-Derived Compounds to Stem the Tide of Multidrug-Resistant Pathogenic Bacteria, Fungi, and Protozoa. Mar Drugs 2020; 18(3): 145.
[http://dx.doi.org/10.3390/md18030145] [PMID: 32121196]

[48] Sueyoshi K, Kaneda M, Sumimoto S, *et al.* Odoamide, a cytotoxic cyclodepsipeptide from the marine cyanobacterium *Okeania* sp. Tetrahedron 2016; 72(35): 5472-8. [https://doi.org/10.1016/j.tet.2016.07.031].
[http://dx.doi.org/10.1016/j.tet.2016.07.031]

[49] Petitbois JG, Casalme LO, Lopez JAV, *et al.* Serinolamides and Lyngbyabellins from an *Okeania* sp. Cyanobacterium Collected from the Red Sea. J Nat Prod 2017; 80(10): 2708-15.
[http://dx.doi.org/10.1021/acs.jnatprod.7b00449] [PMID: 29019684]

[50] Harrigan GG, Yoshida WY, Moore RE, *et al.* Isolation, structure determination, and biological activity of dolastatin 12 and lyngbyastatin 1 from *Lyngbya majuscula/Schizothrix calcicola* cyanobacterial assemblages. J Nat Prod 1998; 61(10): 1221-5.
[http://dx.doi.org/10.1021/np9801211] [PMID: 9784156]

[51] https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/symploca

[52] Phyo MY, Ding CYG, Goh HC, *et al.* Trikoramide A, a Prenylated Cyanobactin from the Marine Cyanobacterium *Symploca hydnoides*. J Nat Prod 2019; 82(12): 3482-8.
[http://dx.doi.org/10.1021/acs.jnatprod.9b00675] [PMID: 31763840]

[53] Ma YP, Ding CYG, Ong JFM, Tan LT. Isolation and Structure Determination of Trikoramide A from the Marine Cyanobacterium *Symploca* sp. 99. Mar Drugs 2020; 18. [Synopsis].

[54] https://accedacris.ulpgc.es/bitstream/10553/74363/2/0767079_00000_0000.pdf

[55] Williams PG, Yoshida WY, Moore RE, Paul VJ. Tasipeptins A and B: new cytotoxic depsipeptides from the marine cyanobacterium *Symploca* sp. J Nat Prod 2003; 66(5): 620-4.
[http://dx.doi.org/10.1021/np020582t] [PMID: 12762794]

[56] Khan MI, Shin JH, Kim JD. The promising future of microalgae: current status, challenges, and optimization of a sustainable and renewable industry for biofuels, feed, and other products. Microb Cell Fact 2018; 17(1): 36.
[http://dx.doi.org/10.1186/s12934-018-0879-x] [PMID: 29506528]

[57] Matos J, Cardoso C, Gomes A, *et al.* Bioprospection of *Isochrysis galbana* and its potential as a nutraceutical. Food Funct 2019; 10(11): 7333-42.
[http://dx.doi.org/10.1039/C9FO01364D] [PMID: 31646314]

[58] Mishra N, Mishra N. Exploring the biologically active metabolites of *Isochrysis galbana* in pharmaceutical interest: An overview. IJPSR 2018; 9: 2162-74. [https://ijpsr.com/articles/].

[59] https://en.wikipedia.org/wiki/Prymnesin-2

[60] Hussein HA, Abdullah MA. Anticancer Compounds Derived from Marine Diatoms. Mar Drugs 2020; 18(7): 356.
[http://dx.doi.org/10.3390/md18070356] [PMID: 32660006]

[61] Gastineau R, Turcotte F, Pouvreau JB, *et al.* Marennine, promising blue pigments from a widespread *Haslea* diatom species complex. Mar Drugs 2014; 12(6): 3161-89.
[http://dx.doi.org/10.3390/md12063161] [PMID: 24879542]

[62] Luo X, Su P, Zhang W. Advances in Microalgae-Derived Phytosterols for Functional Food and Pharmaceutical Applications. Mar Drugs 2015; 13(7): 4231-54.
[http://dx.doi.org/10.3390/md13074231] [PMID: 26184233]

[63] Kim YS, Li XF, Kang KH, Ryu B, Kim SK. Stigmasterol isolated from marine microalgae *Navicula incerta* induces apoptosis in human hepatoma HepG2 cells. BMB Rep 2014; 47(8): 433-8.

[http://dx.doi.org/10.5483/BMBRep.2014.47.8.153] [PMID: 24286323]

[64] Riccio G, Lauritano C. Microalgae with Immunomodulatory Activities. Mar Drugs 2019; 18(1): 2. [http://dx.doi.org/10.3390/md18010002] [PMID: 31861368]

[65] Gabed N, Verret F, Peticca A, *et al.* What Was Old Is New Again: The Pennate Diatom *Haslea ostrearia* (Gaillon) Simonsen in the Multi-Omic Age. Mar Drugs 2022; 20(4): 234. [http://dx.doi.org/10.3390/md20040234] [PMID: 35447907]

[66] de Vera C, Díaz Crespín G, Hernández Daranas A, *et al.* Marine Microalgae: Promising Source for New Bioactive Compounds. Mar Drugs 2018; 16(9): 317. [http://dx.doi.org/10.3390/md16090317] [PMID: 30200664]

[67] Sansone C, Galasso C, Orefice I, *et al.* The green microalga *Tetraselmis suecica* reduces oxidative stress and induces repairing mechanisms in human cells. Sci Rep 2017; 7(1): 41215. [http://dx.doi.org/10.1038/srep41215] [PMID: 28117410]

[68] Munday R, Quilliam MA, LeBlanc P, *et al.* Investigations into the toxicology of spirolides, a group of marine phycotoxins. Toxins (Basel) 2011; 4(1): 1-14. [http://dx.doi.org/10.3390/toxins4010001] [PMID: 22347619]

[69] Martínez KA, Lauritano C, Druka D, *et al.* Amphidinol 22, a New Cytotoxic and Antifungal Amphidinol from the Dinoflagellate *Amphidinium carterae.* Mar Drugs 2019; 17(7): 385. [http://dx.doi.org/10.3390/md17070385] [PMID: 31252576]

[70] Egler RA, Ahuja SP, Matloub Y. L-asparaginase in the treatment of patients with acute lymphoblastic leukemia. J Pharmacol Pharmacother 2016; 7(2): 62-71. [http://dx.doi.org/10.4103/0976-500X.184769] [PMID: 27440950]

[71] Mejía-Camacho AL, Durán-Riveroll LM, Cembella AD. Toxicity Bioassay and Cytotoxic Effects of the Benthic Marine Dinoflagellate *Amphidinium operculatum.* J Xenobiot 2021; 11(2): 33-45. [http://dx.doi.org/10.3390/jox11020003] [PMID: 33925574]

[72] Bauer I, Maranda L, Young KA, *et al.* Isolation and Structure of Caribenolide I, a Highly Potent Antitumor Macrolide from a Cultured Free-Swimming Caribbean Dinoflagellate, *Amphidinium* sp. S1-36-5. J Org Chem 1995; 60(4): 1084-6. [https://doi.org/10.1021/jo00109a050]. [http://dx.doi.org/10.1021/jo00109a050]

[73] Kumagai K, Minamida M, Akakabe M, *et al.* Amphirionin-2, a novel linear polyketide with potent cytotoxic activity from a marine dinoflagellate *Amphidinium* species. Bioorg Med Chem Lett 2015; 25(3): 635-8. [http://dx.doi.org/10.1016/j.bmcl.2014.12.003] [PMID: 25534608]

[74] Washida K, Koyama T, Yamada K, Kita M, Uemura D. Karatungiols A and B, two novel antimicrobial polyol compounds, from the symbiotic marine dinoflagellate *Amphidinium* sp. Tetrahedron Lett 2006; 47(15): 2521-5. [https://doi.org/10.1016/j.tetlet.2006.02.045]. [http://dx.doi.org/10.1016/j.tetlet.2006.02.045]

[75] Akakabe M, Kumagai K, Tsuda M, *et al.* Iriomoteolide-13a, a cytotoxic 22-membered macrolide from a marine dinoflagellate *Amphidinium* species. Tetrahedron 2014; 70(18): 2962-5. [https://doi.org/10.1016/j.tet.2014.03.025]. [http://dx.doi.org/10.1016/j.tet.2014.03.025]

[76] Iwai T, Kubota T, Kobayashi J. Absolute configuration of amphidinin A. J Nat Prod 2014; 77(6): 1541-4. [http://dx.doi.org/10.1021/np5003065] [PMID: 24836179]

[77] Ferrara L. Dinoflagellates Important Marine Producers of Natural Bio-Compounds with High Biotechnological and Pharmacological Potential. Journal of Food Chemistry & Nanotechnology 2020; 6(3): 138-49. [DOI:10.17756/jfcn.2020-095]. [http://dx.doi.org/10.17756/jfcn.2020-095]

[78] Camacho F, Macedo A, Malcata F. Potential Industrial Applications and Commercialization of

Microalgae in the Functional Food and Feed Industries: A Short Review. Mar Drugs 2019; 17(6): 312. [http://dx.doi.org/10.3390/md17060312] [PMID: 31141887]

[79] Vogelstein B, Sur S, Prives C. p53: The Most Frequently Altered Gene in Human Cancers. New Educator 2010; 3: 6. [https://www.nature.com/scitable/topicpage/p53-the-most-frequently-alt-red-gene-in-14192717/#(IARCTP53database)].

[80] Espiña B, Rubiolo JA. Marine toxins and the cytoskeleton: pectenotoxins, unusual macrolides that disrupt actin. FEBS J 2008; 275(24): 6082-8. [http://dx.doi.org/10.1111/j.1742-4658.2008.06714.x] [PMID: 19016860]

[81] Reguera B, Riobó P, Rodríguez F, *et al.* Dinophysis toxins: causative organisms, distribution and fate in shellfish. Mar Drugs 2014; 12(1): 394-461. [http://dx.doi.org/10.3390/md12010394] [PMID: 24447996]

[82] Kim GY, Kim WJ, Choi YH. Pectenotoxin-2 from marine sponges: a potential anti-cancer agent-a review. Mar Drugs 2011; 9(11): 2176-87. [http://dx.doi.org/10.3390/md9112176] [PMID: 22163180]

[83] Soliño L, Sureda FX, Diogène J. Evaluation of okadaic acid, dinophysistoxin-1 and dinophysistoxin-2 toxicity on Neuro-2a, NG108-15 and MCF-7 cell lines. Toxicol In Vitro 2015; 29(1): 59-62. [http://dx.doi.org/10.1016/j.tiv.2014.09.002] [PMID: 25238672]

[84] Ferron PJ, Hogeveen K, Fessard V, Hégarat L. Comparative analysis of the cytotoxic effects of okadaic acid-group toxins on human intestinal cell lines. Mar Drugs 2014; 12(8): 4616-34. [http://dx.doi.org/10.3390/md12084616] [PMID: 25196936]

[85] Afonso TB, Costa MS, Rezende de Castro R, *et al.* Bartolosides E–K from a Marine Coccoid Cyanobacterium. J Nat Prod 2016; 79(10): 2504-13. [http://dx.doi.org/10.1021/acs.jnatprod.6b00351] [PMID: 27680198]

[86] Kim D, Miyazaki Y, Nakashima T, *et al.* Cytotoxic action mode of a novel porphyrin derivative isolated from harmful red tide dinoflagellate *Heterocapsa circularisquama*. J Biochem Mol Toxicol 2008; 22(3): 158-65. [http://dx.doi.org/10.1002/jbt.20216] [PMID: 18561331]

[87] Haguet Q, Bonnet A, Bérard J-B, *et al.* Antimelanoma activity of *Heterocapsa triquetra* pigments. Algal Res 2017; 25: 207-15. [https://doi.org/10.1016/j.algal.2017.04.034]. [http://dx.doi.org/10.1016/j.algal.2017.04.034]

[88] Sugawara T, Yamashita K, Sakai S, *et al.* Induction of apoptosis in DLD-1 human colon cancer cells by peridinin isolated from the dinoflagellate, *Heterocapsa triquetra*. Biosci Biotechnol Biochem 2007; 71(4): 1069-72. [http://dx.doi.org/10.1271/bbb.60597] [PMID: 17420600]

[89] Cai P, He S, Zhou C, *et al.* Two new karlotoxins found in *Karlodinium veneficum* (strain GM2) from the East China Sea. Harmful Algae 2016; 58: 66-73. [http://dx.doi.org/10.1016/j.hal.2016.08.001] [PMID: 28073460]

[90] https://patents.google.com/patent/WO2015090591A1/en

[91] Hwang BS, Yoon EY, Jeong EJ, Park J, Kim EH, Rho JR. Determination of the Absolute Configuration of Polyhydroxy Compound Ostreol B Isolated from the Dinoflagellate *Ostreopsis* cf. *ovata*. J Org Chem 2018; 83(1): 194-202. [http://dx.doi.org/10.1021/acs.joc.7b02569] [PMID: 29185743]

[92] Pelin M, Forino M, Brovedani V, *et al.* Ovatoxin-a, A Palytoxin Analogue Isolated from *Ostreopsis* cf. *ovata* Fukuyo: Cytotoxic Activity and ELISA Detection. Environ Sci Technol 2016; 50(3): 1544-51. [http://dx.doi.org/10.1021/acs.est.5b04749] [PMID: 26714047]

[93] https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/palytoxin

[94] Camacho-Muñoz D, Praptiwi RA, Lawton LA, Edwards C. High Value Phycotoxins From the

Dinoflagellate *Prorocentrum*. Front Mar Sci 2021; 8: 638739. [https://doi.org/10.3389/fmars.2021.638739.]. [http://dx.doi.org/10.3389/fmars.2021.638739]

[95] Sánchez-Suárez J, Garnica-Agudelo M, Villamil L, Díaz L, Coy-Barrera E. Bioactivity and Biotechnological Overview of Naturally Occurring Compounds from the Dinoflagellate Family Symbiodiniaceae: A Systematic Review. ScientificWorldJournal 2021; 1-10. [http://dx.doi.org/10.1155/2021/1983589] [PMID: 34955690]

[96] Selwood AI, Wilkins AL, Munday R, Shi F, Rhodes LL, Holland PT. Portimine: a bioactive metabolite from the benthic dinoflagellate *Vulcanodinium rugosum*. Tetrahedron Lett 2013; 54(35): 4705-7. [https://doi.org/10.1016/j.tetlet.2013.06.098]. [http://dx.doi.org/10.1016/j.tetlet.2013.06.098]

[97] Nézan E, Chomérat N. *Vulcanodinium rugosum* gen. et sp. nov. (Dinophyceae), un Nouveau Dinoflagellé Marin de la Côte Méditerranéenne Française. Cryptogam, Algol 2011; 32(1): 3-18. [https://sciencepress.mnhn.fr/en/periodiques/algologie/32/1/]. [http://dx.doi.org/10.7872/crya.v32.iss1.2011.003]

[98] Geiger M, Desanglois G, Hogeveen K, *et al.* Cytotoxicity, fractionation and dereplication of extracts of the dinoflagellate *Vulcanodinium rugosum*, a producer of pinnatoxin G. Mar Drugs 2013; 11(9): 3350-71. [http://dx.doi.org/10.3390/md11093350] [PMID: 24002102]

[99] Casas-Arrojo V, Decara J, de los Ángeles Arrojo-Agudo M, Pérez-Manríquez C, Abdala-Díaz R. Immunomodulatory, Antioxidant Activity and Cytotoxic Effect of Sulfated Polysaccharides from *Porphyridium cruentum.* (S.F.Gray) Nägeli. Biomolecules 2021; 11(4): 488. [http://dx.doi.org/10.3390/biom11040488] [PMID: 33805009]

[100] Hamann MT. Technology evaluation: Kahalalide F, PharmaMar. Curr Opin Mol Ther 2004; 6(6): 657-65. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4941207/]. [PMID: 15663330]. [PMID: 15663330]

[101] Permatasari HK, Bulain S, Amar N, Rahma M. Anticancer Properties of *Caulerpa racemosa*: A Review Study. Nutr Clín Diet Hosp 2022; 42(3): 110-21. [https://doi.org/10.12873/423permatasari].

[102] Cavas L, Baskin Y, Yurdakoc K, Olgun N. Antiproliferative and newly attributed apoptotic activities from an invasive marine alga: *Caulerpa racemosa* var. *cylindracea*. J Exp Mar Biol Ecol 2006; 339(1): 111-9. [https://avesis.deu.edu.tr/yayin/99d56092-c1a8-4d7f-bc79-8ad5c5d61d60/]. [http://dx.doi.org/10.1016/j.jembe.2006.07.019]

[103] Tanna B, Yadav S, Mishra A. Anti-proliferative and ROS-inhibitory activities reveal the anticancer potential of *Caulerpa* species. Mol Biol Rep 2020; 47(10): 7403-11. [http://dx.doi.org/10.1007/s11033-020-05795-8] [PMID: 32990904]

[104] Senthilkumar D, Jayanthi S. Partial characterization and anticancer activities of purified glycoprotein extracted from green seaweed *Codium decorticatum*. J Funct Foods 2016; 25: 323-32. [https://doi.org/10.1016/j.jff.2016.06.010]. [http://dx.doi.org/10.1016/j.jff.2016.06.010]

[105] Zbakh H, Salhi G, Bochkov V, *et al.* Insights on the anti-inflammatory and antitumor activities of extracts from the marine green alga *Codium decorticatum*. Eur J Integr Med 2020; 37: 101170. [https://doi.org/10.1016/j.eujim.2020.101170]. [http://dx.doi.org/10.1016/j.eujim.2020.101170]

[106] Mofeed J, Deyab M, Sabry AE, Ward F. *In Vitro* Anticancer Activity of Five Marine Seaweeds Extract From Egypt Against Human Breast and Colon Cancer Cell Lines. Res Sq. 2021. [https://doi.org/10.21203/rs.3.rs-462221/v1] [http://dx.doi.org/10.21203/rs.3.rs-462221/v1]

[107] Lomartire S, Gonçalves AMM. An Overview of Potential Seaweed-Derived Bioactive Compounds for Pharmaceutical Applications. Mar Drugs 2022; 20(2): 141.

[http://dx.doi.org/10.3390/md20020141] [PMID: 35200670]

[108] Salindeho N, Nurkolis F, Gunawan WB, Handoko MN, Samtiya M, Muliadi RD. Anticancer and anticholesterol attributes of sea cucumbers: An opinion in terms of functional food applications. Front Nutr 2022; 9: 986986. [https://doi.org/10.3389/fnut.2022.986986].
[http://dx.doi.org/10.3389/fnut.2022.986986]

[109] Cotas J, Pacheco D, Gonçalves AMM, Silva P, Carvalho LG, Pereira L. Seaweeds' nutraceutical and biomedical potential in cancer therapy: a concise review. J Cancer Metastasis Treat 2021; 7: 13. [http://hdl.handle.net/10316/100684].
[http://dx.doi.org/10.20517/2394-4722.2020.134]

[110] Kim RK, Uddin N, Hyun JW, Kim C, Suh Y, Lee SJ. Novel anticancer activity of phloroglucinol against breast cancer stem-like cells. Toxicol Appl Pharmacol 2015; 286(3): 143-50.
[http://dx.doi.org/10.1016/j.taap.2015.03.026] [PMID: 25843036]

[111] Walter LO, Maioral MF, Silva LO, *et al.* Involvement of the NF-κB and PI3K /Akt/ mTOR pathways in cell death triggered by stypoldione, an o-quinone isolated from the brown algae *Stypopodium zonale*. Environ Toxicol 2022; 37(6): 1297-309.
[http://dx.doi.org/10.1002/tox.23484] [PMID: 35128807]

[112] Lins KOAL, Bezerra DP, Alves APNN, *et al.* Antitumor properties of a sulfated polysaccharide from the red seaweed *Champia feldmannii* (Diaz-Pifferer). J Appl Toxicol 2009; 29(1): 20-6.
[http://dx.doi.org/10.1002/jat.1374] [PMID: 18651721]

[113] Arsianti AA, Fadilah F, Suid K, *et al.* Phytochemical composition and anticancer activity of seaweeds *Ulva lactuca* and *Eucheuma cottonii* against breast MCF-7 and colon HCT-116 cells. Asian J Pharm Clin Res 2016; 9(6): 115-9. [http://dx.doi.org/10.22159/ajpcr.2016.v9i6.13798].
[http://dx.doi.org/10.22159/ajpcr.2016.v9i6.13798]

[114] Catarino MD, Fernandes I, Oliveira H, *et al.* Antitumor Activity of *Fucus vesiculosus*-Derived Phlorotannins through Activation of Apoptotic Signals in Gastric and Colorectal Tumor Cell Lines. Int J Mol Sci 2021; 22(14): 7604.
[http://dx.doi.org/10.3390/ijms22147604] [PMID: 34299223]

[115] Omar H, Al-Judaibi A, El-Gendy A. Antimicrobial, Antioxidant, Anticancer Activity and Phytochemical Analysis of the Red Alga, *Laurencia papillosa*. Int J Pharmacol 2018; 14(4): 572-83. [https://scialert.net/fulltext/?doi=ijp.2018.572.583].
[http://dx.doi.org/10.3923/ijp.2018.572.583]

[116] Gross H, Goeger DE, Hills P, *et al.* Lophocladines, bioactive alkaloids from the red alga *Lophocladia* sp. J Nat Prod 2006; 69(4): 640-4.
[http://dx.doi.org/10.1021/np050519e] [PMID: 16643042]

[117] Nitecki S, Strain JJ, Magee PI, McSorley EM, Gill CIR. Anticancer Activity of Raw and Digested Irish *Palmaria palmata* Seaweed on *In Vitro* Models of Colorectal Cancer. Ann Nutr Metab 2012; 61: 322-36. [https://ethos.bl.uk/OrderDetails.do?uin=uk.bl.ethos.673807].

[118] Vajiravelu S, Subbiah M, Sundaresan B, Natarajan TS. *In vitro* cytotoxic studies of red algae *Portieria hornemannii* and *Spyridia fusiformis* against Dalton's lymphoma ascite and Ehrlich ascite carcinoma cell lines. J Coast Life Med 2016; 4(2): 949-52. [https://doi.org/10.12980/jclm.4.2016J6-208].

[119] Gono CMP, Ahmadi P. A Comprehensive Update on the Bioactive Compounds from Seagrasses Mar. Drugs 2022; 20: 97-406.https://pubmed.ncbi.nlm.nih.gov/35877699/

[120] Zhao D, Xie L, Yu L, *et al.* New 2-Benzoxazolinone Derivatives with Cytotoxic Activities from the Roots of *Acanthus ilicifolius*. Chem Pharm Bull (Tokyo) 2015; 63(12): 1087-90.
[http://dx.doi.org/10.1248/cpb.c15-00597] [PMID: 26633031]

[121] Babu BH, Shylesh BS, Padikkala J. Tumour reducing and anticarcinogenic activity of *Acanthus ilicifolius* in mice. J Ethnopharmacol 2002; 79(1): 27-33.
[http://dx.doi.org/10.1016/S0378-8741(01)00347-6] [PMID: 11744292]

[122] Mitra S, Naskar N, Chaudhuri P. A review on potential bioactive phytochemicals for novel therapeutic applications with special emphasis on mangrove species. Phytomedicine Plus 2021; 1(4): 100107. [https://doi.org/10.1016/j.phyplu.2021.100107].
[http://dx.doi.org/10.1016/j.phyplu.2021.100107]

[123] Firdaus M, Prihanto AA, Nurdiani R. Antioxidant and cytotoxic activity of *Acanthus ilicifolius* flower. Asian Pac J Trop Biomed 2013; 3(1): 17-21.
[http://dx.doi.org/10.1016/S2221-1691(13)60017-9] [PMID: 23570011]

[124] Dahibhate NL, Saddhe AA, Kumar K. Mangrove plants as a source of bioactive compounds: a review. J Nat Prod 2019; 9(2): 86-97. [https://doi.org/10.2174/2210315508666180910125328].

[125] Li Y, Dong C, Xu MJ, Lin WH. New alkylated benzoquinones from mangrove plant *Aegiceras corniculatum* with anticancer activity. J Asian Nat Prod Res 2020; 22(2): 121-30.
[http://dx.doi.org/10.1080/10286020.2018.1540604] [PMID: 30614270]

[126] Illian DN, Hasibuan PAZ, Sumardi S, Nuryawan A, Wati R, Basyuni M. Anticancer Activity of Polyisoprenoids from *Avicennia alba* Blume. in WiDr Cells. Iran J Pharm Res 2019; 18(3): 1477-87. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6934958/]. [PMID: 32641956].
[PMID: 32641956]

[127] Dahibhate NL, Kumar K. Metabolite profiling of *Bruguiera cylindrica* reveals presence of potential bioactive compounds. PeerJ Analytical Chemistry 2022; 4: e16. [https://peerj.com/articles/achem-16/].
[http://dx.doi.org/10.7717/peerj-achem.16]

[128] Chaudhry GS, Tengku Muhammad TS, Rahman NH, *et al.* Induction of cytotoxicity by *Bruguiera gymnorrhiza* in human breast carcinoma (MCF-7) cell line *via* activation of the intrinsic pathway. J Adv Pharm Technol Res 2020; 11(4): 233-7.
[http://dx.doi.org/10.4103/japtr.JAPTR_81_20] [PMID: 33425710]

[129] Sultana T, Mitra AK, Das S. Evaluation of anti-cancer potential of *Excoecaria agallocha* (L.) leaf extract on human cervical cancer (SiHa) cell line and assessing the underlying mechanism of action. Future Journal of Pharmaceutical Sciences 2022; 8(1): 3. [https://fjps.springeropen.com/articles/10.1186/s43094-021-00389-y#].
[http://dx.doi.org/10.1186/s43094-021-00389-y]

[130] Venkateswarulu TC, Eswaraiah G, Krupanidhi S, *et al.* Screening of *Ipomoea tuba* Leaf Extract for Identification of Bioactive Constitutes and Evaluation of Its *in vitro* Anti-Proliferative Activity Against MCF-7 and HeLa Cells. Food Technol Biotechnol 2020; 58(1): 71-85.
[http://dx.doi.org/10.17113/ftb.58.01.20.6351] [PMID: 32684790]

[131] Prabhu VV, Guruvayoorappan C. Anti-inflammatory and anti-tumor activity of the marine mangrove *Rhizophora apiculata*. J Immunotoxicol 2012; 9(4): 341-52.
[http://dx.doi.org/10.3109/1547691X.2012.660997] [PMID: 22800297]

[132] Gong KK, Li PL, Qiao D, *et al.* Cytotoxic and Antiviral Triterpenoids from the Mangrove Plant *Sonneratia paracaseolaris*. Molecules 2017; 22(8): 1319.
[http://dx.doi.org/10.3390/molecules22081319] [PMID: 28792469]

[133] Darmadi J, Batubara RR, Himawan S, *et al.* Evaluation of Indonesian mangrove *Xylocarpus granatum* leaves ethyl acetate extract as potential anticancer drug. Sci Rep 2021; 11(1): 6080.https://www.nature.com/articles/s41598-021-85383-3
[http://dx.doi.org/10.1038/s41598-021-85383-3] [PMID: 33727582]

[134] Jing L, Feng L, Zhou Z, *et al.* Limonoid compounds from *Xylocarpus granatum* and their anticancer activity against esophageal cancer cells. Thorac Cancer 2020; 11(7): 1817-26.
[http://dx.doi.org/10.1111/1759-7714.13455] [PMID: 32449599]

[135] Karan S, Turan C, Sangun MK, Eliuz EAE. Bioactive Compounds and Antimicrobial Activity of Glasswort *Salicornia europaea* Indian J Pharm Sci 2021; 83(2): 229-37. [https://www.ijpsonline.com/articles/].

[136] Altay A, Celep GS, Yaprak AE, Baskose I, Bozoglu F. Glassworts as Possible Anticancer Agents Against Human Colorectal Adenocarcinoma Cells with Their Nutritive, Antioxidant and Phytochemical Profiles. Chem Biodivers 2017; 14(3): e1600290.
[http://dx.doi.org/10.1002/cbdv.201600290]

[137] Wu CF, Lee MG, El-Shazly M, *et al.* Isoaaptamine Induces T-47D Cells Apoptosis and Autophagy *via* Oxidative Stress. Mar Drugs 2018; 16(1): 18.
[http://dx.doi.org/10.3390/md16010018] [PMID: 29315210]

[138] Yu H. + 8. Cytotoxic Aaptamine Derivatives from the South China Sea Sponge *Aaptos aaptos* J Nat Prod 2014; 77(9): 2124-9.
[http://dx.doi.org/10.1021/np500583z]

[139] Liu C, Tang X, Li P, Li G, Suberitine A-D. Suberitine A-D, four new cytotoxic dimeric aaptamine alkaloids from the marine sponge *Aaptos suberitoides*. Org Lett 2012; 14(8): 1994-7.
[http://dx.doi.org/10.1021/ol3004589] [PMID: 22472093]

[140] Murniasih T, Putra MY, Bau A, Wibowo JT. A Review on Diversity of Anticancer Compounds Derived from Indonesian Marine Sponges . IOP Conf Ser: Mater Sci Eng.
[https://iopscience.iop.org/article/10.1088/1757-899X/1192/1/012012/meta]

[141] Wilke DV. + 7. Anticancer Potential of Compounds from the Brazilian Blue Amazon. Planta Med 2021; 87(1-02): 49-70.https://pubmed.ncbi.nlm.nih.gov/33142347/

[142] Shakeel S, Dykeman EC, White SJ, *et al.* Genomic RNA folding mediates assembly of human parechovirus. Nat Commun 2017; 8(1): 5.
[http://dx.doi.org/10.1038/s41467-016-0011-z] [PMID: 28232749]

[143] van Kesteren C, de Vooght MMM, López-Lázaro L, *et al.* Yondelis® (trabectedin, ET-743): the development of an anticancer agent of marine origin. Anticancer Drugs 2003; 14(7): 487-502.
[http://dx.doi.org/10.1097/00001813-200308000-00001] [PMID: 12960733]

[144] Anjum K, Abbas SQ, Shah SAA, Akhter N, Batool S, Hassan SS. Marine Sponges as a Drug Treasure. Biomol Ther (Seoul) 2016; 24(4): 347-62.
[http://dx.doi.org/10.4062/biomolther.2016.067] [PMID: 27350338]

[145] Kijjoa A, Wattanadilok R, Herz W, Campos N, Nascimento M, Pinto M. Anticancer activity evaluation of kuanoniamines A and C isolated from the marine sponge *Oceanapia sagittaria*, collected from the Gulf of Thailand. Mar Drugs 2007; 5(2): 6-22.
[http://dx.doi.org/10.3390/md502006] [PMID: 18463725]

[146] Warabi K, Matsunaga S, van Soest RWM, Fusetani N. Dictyodendrins A-E, the first telomerase-inhibitory marine natural products from the sponge *Dictyodendrilla verongiformis*. J Org Chem 2003; 68(7): 2765-70.https://pubmed.ncbi.nlm.nih.gov/12662050/

[147] Tasdemir D, Mallon R, Greenstein M, *et al.* Aldisine alkaloids from the Philippine sponge *Stylissa massa* are potent inhibitors of mitogen-activated protein kinase kinase-1 (MEK-1). J Med Chem 2002; 45(2): 529-32.
[http://dx.doi.org/10.1021/jm0102856] [PMID: 11784156]

[148] Halim H, Chunhacha P, Suwanborirux K, Chanvorachote P. Anticancer and antimetastatic activities of Renieramycin M, a marine tetrahydroisoquinoline alkaloid, in human non-small cell lung cancer cells. Anticancer Res 2011; 31(1): 193-201. [https://pubmed.ncbi.nlm.nih.gov/21273598/]. [PMID: 21273598].
[PMID: 21273598]

[149] Tang WZ, Lu JR, Wang GF, *et al.* New norterpene cyclic peroxides and a new polyketide from the marine sponge *Diacarnus megaspinorhabdosa*. Tetrahedron Lett 2021; 74(22): 153155.
[https://doi.org/10.1016/j.tetlet.2021.153155].
[http://dx.doi.org/10.1016/j.tetlet.2021.153155]

[150] Alarif WM, Al-Lihaibi SS, Ghandourah MA, Orif MI, Basaif SA, Ayyad SEN. Cytotoxic scalarane-

type sesterterpenes from the Saudi Red Sea sponge *Hyrtios erectus*. J Asian Nat Prod Res 2016; 18(6): 611-7.
[http://dx.doi.org/10.1080/10286020.2015.1115019] [PMID: 26630474]

[151] Ahn JH, Woo JH, Rho JR, Choi JH. Anticancer Activity of Gukulenin A Isolated from the Marine Sponge *Phorbas gukhulensis In Vitro* and *In Vivo*. Mar Drugs 2019; 17(2): 126.
[http://dx.doi.org/10.3390/md17020126] [PMID: 30795557]

[152] Kuznetsov G, TenDyke K, Towle MJ, *et al.* Tubulin-based antimitotic mechanism of E7974, a novel analogue of the marine sponge natural product hemiasterlin. Mol Cancer Ther 2009; 8(10): 2852-60.
[http://dx.doi.org/10.1158/1535-7163.MCT-09-0301] [PMID: 19825803]

[153] Arai M, Yamano Y, Fujita M, Setiawan A, Kobayashi M. Stylissamide X, a new proline-rich cyclic octapeptide as an inhibitor of cell migration, from an Indonesian marine sponge of *Stylissa* sp. Bioorg Med Chem Lett 2012; 22(4): 1818-21.
[http://dx.doi.org/10.1016/j.bmcl.2011.10.023] [PMID: 22260773]

[154] Hasin O, Shoham S, Kashman Y, Ilan M, Carmeli S. Theonellamides J and K and 5- *cis*-Apoatheopalauamide, Bicyclic Glycopeptides of the Red Sea Sponge *Theonella swinhoei.* Mar Drugs 2021; 20(1): 31.
[http://dx.doi.org/10.3390/md20010031] [PMID: 35049886]

[155] Govindam SVS, Choi BK, Yoshioka Y, *et al.* Novel cytotoxic polyoxygenated steroids from an Okinawan sponge *Dysidea* sp. Biosci Biotechnol Biochem 2012; 76(5): 999-1002.
[http://dx.doi.org/10.1271/bbb.120017] [PMID: 22738973]

[156] Li J, Wang Z, Yang F, Jiao WH, Lin HW, Xu SH. Two new steroids with cytotoxicity from the marine sponge *Dactylospongia elegans* collected from the South China Sea. Nat Prod Res 2019; 33(9): 1340-4.
[http://dx.doi.org/10.1080/14786419.2018.1475385] [PMID: 29863897]

[157] Trinh TTV. + 7. New 9α-Hydroxy-5α,6α-epoxyhydroxysterols from the Vietnamese Marine Sponge *Ircinia echinata*. Mar Drugs 2018; 16(11): 424.
[http://dx.doi.org/10.3390/md16110424] [PMID: 30388820]

[158] Mun B. + 13. Cytotoxic 5α,8α-epidioxy sterols from the marine sponge *Monanchora* sp. Arch Pharm Res 2015; 38(1): 18-25.
[http://dx.doi.org/10.1007/s12272-014-0480-8] [PMID: 25231340]

[159] Pailee P, Mahidol C, Ruchirawat S, Prachyawarakorn V. Sterols from Thai Marine Sponge *Petrosia (Strongylophora)* sp. and Their Cytotoxicity. Mar Drugs 2017; 15(3): 54.
[http://dx.doi.org/10.3390/md15030054] [PMID: 28241489]

[160] Li J, Tang H, Kurtán T, *et al.* Swinhoeisterols from the South China Sea Sponge *Theonella swinhoei*. J Nat Prod 2018; 81(7): 1645-50.
[http://dx.doi.org/10.1021/acs.jnatprod.8b00281] [PMID: 29989811]

[161] Rodríguez J, Jiménez C, Blanco M, Tarazona G, Fernández R, Cuevas C. Lanesoic Acid: A Cytotoxic Zwitterion from *Theonella* sp. Org Lett 2016; 18(22): 5832-5.
[http://dx.doi.org/10.1021/acs.orglett.6b02832] [PMID: 27802052]

[162] Lai KH, Peng BR, Su CH, *et al.* Anti-Proliferative Potential of Secondary Metabolites from the Marine Sponge *Theonella* sp.: Moving from Correlation toward Causation. Metabolites 2021; 11(8): 532.
[http://dx.doi.org/10.3390/metabo11080532] [PMID: 34436473]

[163] Chen M, Wu XD, Zhao Q, Wang CY. Topsensterols A–C, Cytotoxic Polyhydroxylated Sterol Derivatives from a Marine Sponge *Topsentia* sp. Mar Drugs 2016; 14(8): 146.
[http://dx.doi.org/10.3390/md14080146] [PMID: 27490555]

[164] El-Gamal A, Al-Massarani S, Shaala L, *et al.* Cytotoxic Compounds from the Saudi Red Sea Sponge *Xestospongia testudinaria*. Mar Drugs 2016; 14(5): 82.

[http://dx.doi.org/10.3390/md14050082] [PMID: 27128926]

[165] Iguchi K, Shimura H, Taira S, Yokoo C, Matsumoto K, Yamada Y. Aragusterol B and D, new 26,27-cyclosterols from the Okinawan marine sponge of the genus *Xestospongia*. J Org Chem 1994; 59(24): 7499-502. [https://doi.org/10.1021/jo00103a053].
[http://dx.doi.org/10.1021/jo00103a053]

[166] Chantarawong W, Chamni S, Suwanborirux K, Saito N, Chanvorachote P. 5-O-Acetyl-Renieramycin T from Blue Sponge drug sources: chemical and biological aspects. Acta Pharm Sin B 2019; 9(2): 237-57.
[http://dx.doi.org/10.1016/j.apsb.2018.10.003] [PMID: 30972275]

[167] Ortega V, Cortés J. Potential clinical applications of halichondrins in breast cancer and other neoplasms. Breast Cancer (Dove Med Press) 2012; 4: 9-19. [https://pubmed.ncbi.nlm.nih.gov/24367189/]. [PMID: 24367189].
[PMID: 24367189]

[168] McBride A, Butler SK. Eribulin mesylate: A novel halichondrin B analogue for the treatment of metastatic breast cancer. Am J Health Syst Pharm 2012; 69(9): 745-55.
[http://dx.doi.org/10.2146/ajhp110237] [PMID: 22517020]

[169] Roll DM, Scheuer PJ, Matsumoto GK, Clardy J. Halenaquinone, a pentacyclic polyketide from a marine sponge. J Am Chem Soc 1983; 105(19): 6177-8. [https://doi.org/10.1021/ja00357a049].
[http://dx.doi.org/10.1021/ja00357a049]

[170] Jimenez PC, Wilke DV, Costa-Lotufo LV. Marine drugs for cancer: surfacing biotechnological innovations from the oceans. Clinics (São Paulo) 2018; 73 (Suppl. 1): e482s.
[http://dx.doi.org/10.6061/clinics/2018/e482s] [PMID: 30133563]

[171] Schwartsmann G, da Rocha AB, Berlinck RGS, Jimeno J, Oncol L. Marine organisms as a source of new anticancer agents. Lancet Oncol 2001; 2(4): 221-5.
[http://dx.doi.org/10.1016/S1470-2045(00)00292-8] [PMID: 11905767]

[172] Hunt ME, Modi CK, Aglyamova GV, Ravikant DVS, Meyer E, Matz MV. Multi-domain GFP-like proteins from two species of marine hydrozoans. Photochem Photobiol Sci 2012; 11(4): 637-44.
[http://dx.doi.org/10.1039/c1pp05238a] [PMID: 22251928]

[173] Kawabata T, Lindsay DJ, Kitamura M, *et al.* Evaluation of the bioactivities of water-soluble extracts from twelve deep-sea jellyfish species. Fish Sci 2013; 79(3): 487-94. [https://doi.org/10.1007/s12562-013-0612-y].
[http://dx.doi.org/10.1007/s12562-013-0612-y]

[174] Mariottini G, Pane L. Cytotoxic and cytolytic cnidarian venoms. A review on health implications and possible therapeutic applications. Toxins (Basel) 2013; 6(1): 108-51.
[http://dx.doi.org/10.3390/toxins6010108] [PMID: 24379089]

[175] Korsmo KA. Isolation and characterization of bioactive compounds from the marine hydrozoans *Halecium muricatum* and *Halecium beanie*. 2012. [https://munin.uit.no/bitstream/handle/10037/4327/thesis.pdf?sequence=2]

[176] Sala S, Micke SK, Flematti GR. Marine Natural Products from Flora and Fauna of the Western Australian Coast: Taxonomy, Isolation and Biological Activity. Molecules 2023; 28(3): 1452.
[http://dx.doi.org/10.3390/molecules28031452] [PMID: 36771114]

[177] Kang C, Munawir A, Cha M, *et al.* Cytotoxicity and hemolytic activity of jellyfish *Nemopilema nomurai* (Scyphozoa: Rhizostomeae) venom. Comp Biochem Physiol C Toxicol Pharmacol 2009; 150(1): 85-90.
[http://dx.doi.org/10.1016/j.cbpc.2009.03.003] [PMID: 19303056]

[178] Su YD, Su JH, Hwang TL, *et al.* Briarane Diterpenoids Isolated from Octocorals between 2014 and 2016. Mar Drugs 2017; 15(2): 44.
[http://dx.doi.org/10.3390/md15020044] [PMID: 28218675]

[179] Xio YJ, Su JH, Chen BW, Tseng YJ, Wu YC, Sheu JH. Oxygenated ylangene-derived sesquiterpenoids from the soft coral *Lemnalia philippinensis*. Mar Drugs 2013; 11(10): 3735-41. [http://dx.doi.org/10.3390/md11103735] [PMID: 24084789]

[180] Moritz M, Marostica L, Bianco É, *et al.* Polyoxygenated steroids from the octocoral *Leptogorgia punicea* and *in vitro* evaluation of their cytotoxic activity. Mar Drugs 2014; 12(12): 5864-80. [http://dx.doi.org/10.3390/md12125864] [PMID: 25486111]

[181] Ng SY, Phan CS, Ishii T, Kamada T, Hamada T, Vairappan CS. Terpenoids from Marine Soft Coral of the Genus *Xenia* in 1977 to 2019. Molecules 2020; 25(22): 5386. [http://dx.doi.org/10.3390/molecules25225386] [PMID: 33217924]

[182] Ciavatta ML, Lefranc F, Carbone M, *et al.* Marine Mollusk-Derived Agents with Antiproliferative Activity as Promising Anticancer Agents to Overcome Chemotherapy Resistance. Med Res Rev 2017; 37(4): 702-801. [http://dx.doi.org/10.1002/med.21423] [PMID: 27925266]

[183] Santhanam R, Ramesh S, David SR. Biology and Ecology of Pharmaceutical Marine Life: Echinoderms (Series: Biology and Ecology of Pharmaceutical Marine Life) CRC Press. USA: Taylor & Francis 2019. c[https://www.taylorfrancis.com/books/mono/10.1201/9780429060236/] [http://dx.doi.org/10.1201/9780429060236]

[184] Azad N, Najdegerami EH, Imani M, Nikoo M. Bioactive peptides from the Pacific white-leg shrimp (*Litopenaeus vannamei*) induce apoptosis and anticancer activities in HCT-116 colon cancer cell line. Iran J Fish Sci 2022; 21(5): 1180-91. [http://jifro.ir/browse.php?a_code=A-10-25-9-2&slc_lang=en&sid=1].

[185] Behera A, Das R, Patnaik P, Mohanty J, Mohanty G. A review on fish peptides isolated from fish waste with their potent bioactivities. J Appl Biol Biotechnol 2022; 10(03): 195-209. [http://dx.doi.org/10.7324/JABB.2022.100323]

[186] Kannan A, Hettiarachchy NS, Marshall M, Raghavan S, Kristinsson H. Shrimp shell peptide hydrolysates inhibit human cancer cell proliferation. J Sci Food Agric 2011; 15;91(10): 1920-4.

[187] Priya ER, Ravichandr S. Anti Cancer Compounds of *Calappa calappa* L. (1758). International Journal of Zoological Research 2015; 11(3): 107-11. [https://scialert.net/fulltext/?doi=ijzr.2015.107.111]. [http://dx.doi.org/10.3923/ijzr.2015.107.111]

[188] Doyen A, Beaulieu L, Saucier L, Pouliot Y, Bazinet L. Demonstration of *in vitro* anticancer properties of peptide fractions from a snow crab by-products hydrolysate after separation by electrodialysis with ultrafiltration membranes. Separ Purif Tech 2011; 78(3): 321-9. [https://doi.org/10.1016/j.seppur.2011.01.037]. [http://dx.doi.org/10.1016/j.seppur.2011.01.037]

[189] Kavitha R. Aiswarya s, Ratnavali CMG. Anticancer activity of red pigment from *Serratia marcescens* in Human cervix carcinoma. Int J Pharm Tech Res 2010; 2(1): 784-7. [https://sphinxsai.com/sphinxsaivol_2no.1/pharmtech_vol_2no.1/PharmTech_Vol_2No.1PDF/PT=120%20(784-787).pdf].

[190] Baharlouei P, Rahman A. Chitin and Chitosan. Mar Drugs 2022; 20(7): 460. [http://dx.doi.org/10.3390/md20070460] [PMID: 35877753]

[191] Hadrian E, Sari AP, Mayanti T, *et al.* Steroids from *Atactodea striata* and Their Cytotoxic Activity against MCF-7 Breast Cancer Cell Lines. Indonesian Journal of Chemistry 2022; 23(1): 200-9. [https://doi.org/10.22146/ijc.76438]. [http://dx.doi.org/10.22146/ijc.76438]

[192] Odeleye T, White W, Lu J. Cytotoxicity of Extracts from New Zealand Surf Clams Against Organ Cancer Cell Lines. Biomedicines 2019; 7(2): 25. [http://dx.doi.org/10.3390/biomedicines7020025] [PMID: 30935008]

[193] Cheong SH, Kim EK, Hwang JW, *et al.* Purification of a novel peptide derived from a shellfish,

Crassostrea gigas, and evaluation of its anticancer property. J Agric Food Chem 2013; 61(47): 11442-6.
[http://dx.doi.org/10.1021/jf4032553] [PMID: 24199654]

[194] Honari M, Tehranifard A, Vazirian M, Salaritabar A, Sanati H, Ansari AM. Cytotoxic Effect of *Turbo coronatus* Extract on Cancer Cell Lines. RRJPPS 2017; 6(1): 55-8. [https: //doi.org /10.3390/ antiox12020386].

[195] Tortorella E, Giugliano R, De Troch M, Vlaeminck B, de Viçose GC, de Pascale D. The Ethyl Acetate Extract of the Marine Edible Gastropod *Haliotis tuberculata* coccinea: a Potential Source of Bioactive Compounds. Mar Biotechnol (NY) 2021; 23(6): 892-903.
[http://dx.doi.org/10.1007/s10126-021-10073-0] [PMID: 34714443]

[196] Jeyasanta I, Patterson J. Bioactive Properties of Ink Gland Extract from Squid *Loligo duvauceli*. Ecología (Madr) 2019; 10(1): 9-19. [https://scialert.net/abstract/?doi=ecologia.2020.9.19].
[http://dx.doi.org/10.3923/ecologia.2020.9.19]

[197] Hernández-Zazueta MS, Luzardo-Ocampo I, García-Romo JS, *et al.* Bioactive compounds from *Octopus vulgaris* ink extracts exerted anti-proliferative and anti-inflammatory effects *in vitro*. Food Chem Toxicol 2021; 151: 112119.
[http://dx.doi.org/10.1016/j.fct.2021.112119] [PMID: 33722603]

[198] Lazzara V, Arizza V, Luparello C, Mauro M, Vazzana M. Bright Spots in The Darkness of Cancer: A Review of Starfishes-Derived Compounds and Their Anti-Tumor Action. Mar Drugs 2019; 17(11): 617.
[http://dx.doi.org/10.3390/md17110617] [PMID: 31671922]

[199] Baharara J, Amini E. The Potential of Brittle Star Extracted Polysaccharide in Promoting Apoptosis *via* Intrinsic Signaling Pathway. Avicenna J Med Biotechnol 2015; 7(4): 151-8.
[PMID: 26605009]

[200] Klimenko A, Rodina EE, Silachev D, *et al.* Chlorin Endogenous to the North Pacific Brittle Star *Ophiura sarsii* for Photodynamic Therapy Applications in Breast Cancer and Glioblastoma Models. Biomedicines 2022; 10(1): 134.
[http://dx.doi.org/10.3390/biomedicines10010134] [PMID: 35052813]

[201] Thao NP, Luyen BTT, Kim EJ, *et al.* Steroidal constituents from the edible sea urchin *Diadema savignyi* Michelin induce apoptosis in human cancer cells. J Med Food 2015; 18(1): 45-53.
[http://dx.doi.org/10.1089/jmf.2013.3105] [PMID: 25211186]

[202] Brasseur L, Hennebert E, Fievez L, *et al.* The Roles of Spinochromes in Four Shallow Water Tropical Sea Urchins and Their Potential as Bioactive Pharmacological Agents. Mar Drugs 2017; 15(6): 179.
[http://dx.doi.org/10.3390/md15060179] [PMID: 28621734]

[203] Mishchenko NP, Vasileva EA, Gerasimenko AV, Grigorchuk VP, Dmitrenok PS, Fedoreyev SA. Isolation and Structure Determination of Echinochrome A Oxidative Degradation Products. Molecules 2020; 25(20): 4778.
[http://dx.doi.org/10.3390/molecules25204778] [PMID: 33080948]

[204] Russo G, Russo M, Castellano I, Napolitano A, Palumbo A. Ovothiol isolated from sea urchin oocytes induces autophagy in the Hep-G2 cell line. Mar Drugs 2014; 12(7): 4069-85.
[http://dx.doi.org/10.3390/md12074069] [PMID: 25003791]

[205] Sahara H, Ishikawa M, Takahashi N, *et al. In vivo* anti-tumour effect of 3′-sulphonoquinovosyl 1′-monoacylglyceride isolated from sea urchin (*Strongylocentrotus intermedius*) intestine. Br J Cancer 1997; 75(3): 324-32.
[http://dx.doi.org/10.1038/bjc.1997.54] [PMID: 9020475]

[206] Wang H, Wang M, Chen J, *et al.* A polysaccharide from Strongylocentrotus nudus eggs protects against myelosuppression and immunosuppression in cyclophosphamide-treated mice. Int Immunopharmacol 2011; 11(11): 1946-53.
[http://dx.doi.org/10.1016/j.intimp.2011.06.006] [PMID: 21723424]

[207] Wu L, Yang X, Duan X, Cui L, Li G. Exogenous expression of marine lectins DlFBL and SpRBL induces cancer cell apoptosis possibly through PRMT5-E2F-1 pathway. Sci Rep 2014; 4(1): 4505. [http://dx.doi.org/10.1038/srep04505] [PMID: 24675921]

[208] Hou Y, Vasileva EA, Carne A, McConnell M, El-Din A Bekhit A, Mishchenko NP. Naphthoquinones of the spinochrome class: occurrence, isolation, biosynthesis and biomedical applications. RSC Advances 2018; 8(57): 32637-50. [http://dx.doi.org/10.1039/C8RA04777D] [PMID: 35547692]

[209] Wätjen W, Ebada SS, Bergermann A, *et al.* Cytotoxic effects of the anthraquinone derivatives 1′-deoxyrhodoptilometrin and (S)-(−)-rhodoptilometrin isolated from the marine echinoderm *Comanthus* sp. Arch Toxicol 2017; 91(3): 1485-95. [http://dx.doi.org/10.1007/s00204-016-1787-7] [PMID: 27473261]

[210] Nagle DG, Zhou YD. Marine natural products as inhibitors of hypoxic signaling in tumors. Phytochem Rev 2009; 8(2): 415-29. [http://dx.doi.org/10.1007/s11101-009-9120-1] [PMID: 20622986]

[211] Ebada S, Wray V, Edrada R, Proksch P. Anthraquinones and naphthopyrones from the marine echinoderm *Comanthus* sp. Planta Med 2009; 75(9): 75-PE11. [https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0029-1234572]. [http://dx.doi.org/10.1055/s-0029-1234572]

[212] Khokhar S, Pierens GK, Hooper JNA, Ekins MG, Feng Y, Davis RA. Rhodocomatulin-Type Anthraquinones from the Australian Marine Invertebrates *Clathria hirsuta* and *Comatula rotalaria*. J Nat Prod 2016; 79(4): 946-53. [http://dx.doi.org/10.1021/acs.jnatprod.5b01029] [PMID: 27063022]

[213] Yun SH, Sim EH, Han SH, *et al.* Holotoxin A1 Induces Apoptosis by Activating Acid Sphingomyelinase and Neutral Sphingomyelinase in K562 and Human Primary Leukemia Cells. Mar Drugs 2018; 16(4): 123. [http://dx.doi.org/10.3390/md16040123] [PMID: 29642569]

[214] Janakiram N, Mohammed A, Rao C. Sea Cucumbers Metabolites as Potent Anti-Cancer Agents. Mar Drugs 2015; 13(5): 2909-23. [http://dx.doi.org/10.3390/md13052909] [PMID: 25984989]

[215] Mashjoor S, Yousefzad M, Pishevarzad F. Assessment of anticancer potential of selected *Holothuria* species. Indian J Tradit Knowl 2019; 18(2): 272-80. [https://core.ac.uk/download/pdf/297999269.pdf].

[216] Zhang JJ, Zhu KQ. A novel antitumor compound nobiliside D isolated from sea cucumber (*Holothuria nobilis* Selenka). Exp Ther Med 2017; 14(2): 1653-8. [http://dx.doi.org/10.3892/etm.2017.4656] [PMID: 28810632]

[217] Zou ZR, Yi YH, Wu HM, Wu JH, Liaw CC, Lee KH. Intercedensides A-C, three new cytotoxic triterpene glycosides from the sea cucumber *Mensamaria intercedens* Lampert. J Nat Prod 2003; 66(8): 1055-60. [http://dx.doi.org/10.1021/np030064y] [PMID: 12932123]

[218] Zou Z, Yi Y, Wu H, *et al.* Intercedensides D-I, cytotoxic triterpene glycosides from the sea cucumber *Mensamaria intercedens* Lampert. J Nat Prod 2005; 68(4): 540-6. [http://dx.doi.org/10.1021/np040205b] [PMID: 15844944]

[219] Wargasetia TL, Ratnawati H, Widodo N. Sea Cucumber Compounds Targeting NF-κB in Cancer Treatment. Bioinform Biol Insights 2022; 16 [http://dx.doi.org/10.1177/11779322221091740] [PMID: 35462875]

[220] Santhanam R, Ramesh S, Nivedhitha S, Balasundari S. Pharmaceuticals and Nutraceuticals from Fish and Fish Wastes. USA: Apple Academic Press 2022. [https://www.appleacademicpress.com/pharmaceuticals-and-nutraceuticals-from-fish-and-fish-wastes-/9781774630105]

[http://dx.doi.org/10.1201/9781003180548]

[221] Palanisamy SK, Rajendran NM, Marino A. Natural Products Diversity of Marine Ascidians (Tunicates; Ascidiacea) and Successful Drugs in Clinical Development. Nat Prod Bioprospect 2017; 7(1): 1-111.
[http://dx.doi.org/10.1007/s13659-016-0115-5] [PMID: 28097641]

[222] Vervoort H, Fenical W, Epifanio RA. Tamandarins A and B: new cytotoxic depsipeptides from a Brazilian ascidian of the family Didemnidae. J Org Chem 2000; 65(3): 782-92.
[http://dx.doi.org/10.1021/jo991425a] [PMID: 10814011]

[223] Badre A, Boulanger A, Abou-Mansour E, Banaigs B, Combaut G, Francisco C. Eudistomin U and isoeudistomin U, new alkaloids from the Caribbean ascidian *Lissoclinum fragile*. J Nat Prod 1994; 57(4): 528-33.
[http://dx.doi.org/10.1021/np50106a016] [PMID: 8021654]

[224] Nurdiani R, Vasiljevic T, Singh TK, Donkor ON. ON. Bioactive peptides from fish by-products with anticarcinogenic potential. Int Food Res J 2017; 4(5): 1840-9.https://www.cabdirect.org/cabdirect/abstract/20183067238

[225] Pangestuti R, Kim SK. Bioactive Peptide of Marine Origin for the Prevention and Treatment of Non-Communicable Diseases. Mar Drugs 2017; 15(3): 67.
[http://dx.doi.org/10.3390/md15030067] [PMID: 28282929]

[226] https://clinicaltrials.gov/ct2/show/NCT0000599

[227] Varier KM, Chinnasamy A, Gajendran B, Nagarathnam R. Isolation and characterization of a novel anticancer muscle protein from edible marine catfish *Tachysurus dussumeiri*. Int J Pharm Sci Res 2018; 9: 2720-30. [http://dx.doi.org/10.13040/IJPSR.0975-8232.9(7).2720-30].

[228] Oda T, Fujiwara T, Liu H, *et al.* Effects of Lissoclibadins and Lissoclinotoxins, Isolated from a Tropical Ascidian *Lissoclinum cf. badium*, on IL-8 production in a PMA-stimulated Promyelocytic Leukemia Cell Line. Mar Drugs 2006; 4(1): 15-21.
[http://dx.doi.org/10.3390/md401015]

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