Marine Biotechnology and its potentials in cancer treatment: Review article

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(Received 28 Sep, 2013 Accepted 17 Jun, 2014)

Review Article

Abstract

Marine environment has unique diversity. More than half of biodiversity lives at sea and oceans. Promotion of science and technology led to the future accession to marine species and study them and finally using marine product in human life. Using marine product for treatment of human malady is one of the most attractive applications of this component. Since cancer is the second mortality agent in human and current drugs has several side effects, identification and isolation of anti-cancer component from marine source is one of the most attractive research branches for scientists. The aim of this study is investigation of marine components which used in cancer treatment. In this article, we point to some of anti-cancer and drugs with FDA approve or component that are in different stage of clinical trials. The source of them and their mechanism were investigated too. Despite of an existing variety of fresh and brine source in Iran, there isn't any spacious study for identification, isolation, investigation and confirmation of remedial, and especially anti-cancer property of marine source. Thus attend to marine source in order to cancer treatment is very necessary.

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Key words: Biotechnology, Cancer, Marine Source, Treatment

Citation: Aghamollaei H, Latifi AM, Najafi A. Marine Biotechnology and its potentials in cancer treatment: Review article. Hormozgan Medical Journal 2016;19(6):376-384.

Introduction:

Biotech is defined as the use of biological processes or organisms in manufacturing or services. Biotech is considered as an interdisciplinary science in terms of the inherent characteristics. This field can be divided into three periods: The first period is called the ancient one; human beings produced fermentation products such as vinegar, bread, dairy products, alcoholic beverages, pickles, etc. without knowing the details of biological processes (1). The second period was associated with the expansion of human knowledge about the mechanisms of growth and survival of organisms and began with the design of appropriate conditions, production of metabolites such as antibiotics, enzymes, presence of nutrients, organic chemicals and other compounds in a high volume. New era of biotechnology began with discovering the structure of DNA (2) and transferring genes from one species to another (3) and is now expanding by the sciences such as genetic engineering, biochemistry, genomics, proteomics and bioinformatics.

The four main branches of biotechnology include agriculture, medicine, industry and the environment. Among them, medical biotechnology has been accompanied by a significant growth (4).

A variety of different drugs, vaccines, and biotechnology-based diagnostic kits is sold in the

market. Most current drugs and bioactive materials are derived from microbial and plant sources and the use of the water environment covering a large part of the Earth's surface is almost neglected. Special attention has been paid to the sea in Islamic sources so that the word "sea" appears 35 times in the Qur'an and the unique characteristics of the seas are stated in different verses.

Marine Biology

The waters have covered more than 70 percent of the Earth's surface. The seas and oceans provide a huge source of food and energy. More than 60 percent of the food of the people living in tropical countries is provided by the sea. Moreover, fish and other sea products are a source of providing animal protein for over a billion people. The life of every human being on earth directly depends on the seas and oceans because about half of the oxygen that people breathe is produced by plankton. The ocean's special functions include weather balance, avoiding the extreme changes in biosphere temperature, and moisture supply for creatures on earth (4). Thus, Attention to them makes clear the importance of this environment. Features such as salt concentration, PH, dose and pressure are very diverse in the ocean. Hence, there is a wide range of creatures with the different and unique characteristics in the ocean.

There are 230,000 different species of plants and animals and thousand microorganisms in the water and it is predicted that there are millions of unknown species in seas and oceans. Now, the known biodiversity in aquatic environments is almost equivalent to the land creatures (5). Different systems of feeding, defending, and communications are unique to sea creatures and seen in the aquatic environment. Scientists study them and draw inspiration from these mechanisms to use them in the human life. Problems such as lack of access to all parts of the seas, inadequate amounts of samples, and the lack of growth for many marine organisms in laboratories cause a delay or sometimes make the research on sea creatures impossible (6).

Marine products such as agar, alginate, (7,8) collagen, chitosan (9), a variety of peptides (10,11) and lipids are isolated from marine organisms and use in various fields such as food and energy supply; environmental decontamination, monitoring, and supplying the required materials for industry, health and human health. For example, in the study conducted by Latifi and others, the alginate extracted from seaweed in the Persian Gulf was used for decontamination of radioactive elements (12). Turnover of seafood is now 2.4 billion dollars and 10% is annually added to it (13). One of the main uses of marine resources is extracting machinery ingredients. Therefore, further studies in this field are being done in different parts of the world. From 1996 to 2006, more than 666 combinations of marine organisms were isolated that had medicinal properties. These drug combinations had properties including anti-bacterial, anti-fungal, anti-viral, reducing inflammation, impact on cardiovascular, endocrine, and immune (14-18). Among them, marine sponges had the highest proportion (38%) in the production of pharmaceutically active compounds (19). After sponges, corals (21%) and microorganisms (15%) had the highest proportion of drug compounds. researchers managed to extract bioactive composition through types of molluscs, crustaceans, green and red Alka and other creatures. Iran also has a special potential for the extraction of bioactive compounds from water resources. According to in the Indo-Pacific Molluscan Database (OBIS), mollusk identified 172 out of 611 genera/species in the Persian Gulf coasts and islands have bioactive compounds. Extraction and purification of antimicrobial agents were carried out from 11 genera/species of mollusk in the Persian Gulf (20). Six mollusks had products affecting the immune system; two mollusks had cardiotonic compounds affecting the vascular system; one mollusk had analgesic compounds and four mollusks had lipid-lowering products for the blood. In addition, some species were detected with products affecting osteoporosis and the activator for osteoblasts and dermatitis (21). According to the identified species in the Persian Gulf with recorded examples in various databases, there are eight species in the Persian Gulf having the anti-cancer activity. These compounds have diverse chemical structures such as peptides, polysaccharides, glycoprotein and cerebroside. A variety of mechanisms, including induction of apoptosis, cytoskeletal structure degradation, affect the

immune system and topoisomerase debarment (19-22).

Anti-cancer compounds from marine sources

In 2012, there were approximately 85,000 cancer patients. It shows a high growth in Iran over the past years. Reasons for the increase in cancer in Iran include increasing the use of chemical pesticides in agricultural products, air pollution, nutrition style change, increasing urbanization and decreasing mobility, increasing psychological pressures and an increase in average life expectancy. The common cancers in Iranian women include breast, skin, colon, stomach, esophagus and the common cancers in Iranian men include stomach, bladder, prostate, colon and blood (23). In the case of gastric cancer in men, the average number of patients in Iran is higher than the global average. (26.1 persons per 100,000) (25).

Although drugs in the world could save a lot of patients, but these drugs have many side effects and are not effective for some types of advanced cancers. Researchers around the world are trying to find more effective drugs with fewer side effects for the treatment of these diseases. Therefore, the use of sea creatures is one of the attractive options for scientists. Between 1996 and 2007, 592 combinations of anti-tumor or toxic for cells were isolated from marine organisms, and cytotoxicity effects were confirmed in the laboratory scale. There are many methods to obtain the compounds through marine resources, including open cultured marine invertebrates (such as ET-743 and Bryostatins), perfect synthesis of these compounds (such as Ziconotide, Discodermolide, and hemicellulose Easterlin), semi-synthetic (such as Halichondrin B), and microbial fermentation (such as thiocoraline) (26). These compounds with different mechanisms are able to inhibit cancer cells. A number of these compounds are mentioned in the following table.A number of compounds with the marine origin have been examined in various clinical stages and are used to treat cancer. In addition, several anti-cancer drugs originated from the sea will be mentioned in different phases of clinical trials.

Cytarabin

Cytarabine or cytosine arabinoside is also known as ara-C (arabinofuranosyl cytidine). It is a chemotherapy agent used mainly in the treatment of cancers of white blood cells such as acute myeloid leukemia (AML) and non-Hodgkin lymphoma (27,28). It kills cancer cells by interfering with DNA synthesis. It was approved by the United States Food and Drug Administration in June 1969, and was initially marketed in the U.S. by Upjohn under the trade name Cytosar-U. It is called cytosine arabinoside because it combines a cytosine base with an arabinose sugar. Cytosine normally combines with a different sugar, deoxyribose, to form deoxycytidine, a component of DNA. Certain sponges, where it was originally found, use arabinoside sugars to form a different compound (not part of DNA). Cytosine arabinoside is similar enough to human cytosine deoxyribose (deoxycytidine) to be incorporated into human DNA, but different enough that it kills the cell. This mechanism is used to kill cancer cells. Cytarabine is the first of a series of cancer drugs that altered the sugar component of nucleosides. Other cancer drugs modify the base (29).

Trabectedin

Trabectedin (also known as ecteinascidin 743 or ET-743) is an anti-tumor drug. It is sold by Zeltia and Johnson and Johnson under the brand name Yondelis. It is also undergoing clinical trials for the treatment of breast, prostate, and paediatric sarcomas. The European Commission and the U.S. Food and Drug Administration (FDA) have granted orphan drug status to trabectedin for soft tissue sarcomas and ovarian cancer. During the 1950s and 1960s, the National Cancer Institute carried out a wide ranging program of screening plant and marine organism material. As part of that program extract from the sea squirt Ecteinascidia turbinata was found to have anticancer activity in 1969 (30).

Recently, it has been shown that Trabectedin blocks DNA binding of the oncogenic transcription factor FUS-CHOP and reverses the transcriptional program in myxoid liposarcoma. By reversing the genetic program created by this transcription factor, Trabectedin promotes differentiation and reverses the oncogenic phenotype in these cells (31). Other than transcriptional interference, the mechanism of action of Trabectedin is complex and not completely understood. The compound is known to bind and alkylate DNA at the N2 position of guanine.

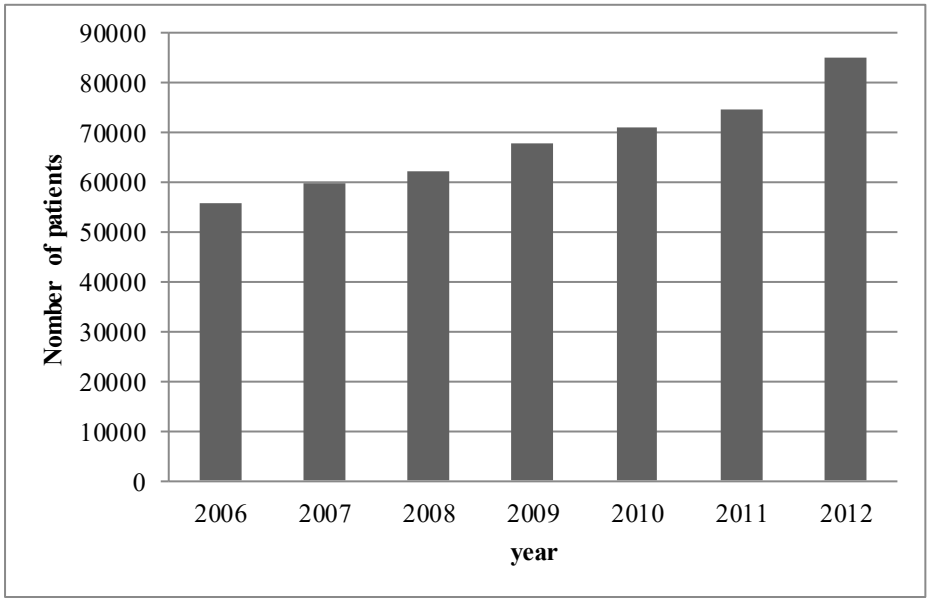

Figure 1. Comparing the number of cancer patients in Iran from 2006 to 2012: as displayed, the number of patients had been associated with an increasing growth

Table 1. Mechanism of action, chemical classes, and resources of anticancer compounds with the origin of marine life

Compound name	Chemical class	Mechanism of action	Resource
DMMC	Cyclic depsipeptide	Inhibition of microtubules polymerization	Cyanobacteria
Sorbicillactone-A	-Lactone - -lactam	Anti-leukemia cells	Sponge
HT1286	Dipeptide	Interfering with the function of microtubules	Sponge
ES-285	Alkyl amino alcohol	Induction of apoptosis	mollusc
LAF389	Amino acid derivative	Methionine amino peptidase inhibitor	Sponge
Thiocoraline	Depsipeptide	Inhibition of DNA polymerase alpha	Actinomycete
Discodermolide	Polyketide	Connecting and stabilizing tubulin	Sponge
Sarcodictiyn	Terpen	Connecting and stabilizing tubulin	Sponge
Plitidepsin	Depsipeptide	Induction of apoptosis	Tawnykit
Tasidotin	Peptide	Interfering with the function of microtubules	Bacteria
NSC 630176	Bicyclic peptide	Inhibition of histone acetylation	Cyanobacteria
MarizomibSalinosporamid-A	Lactam	Proteasome inhibition	Bacteria
Agosterol A	Polyhydroxylated sterol	Inhibition of drug resistance	Sponge
Plinabulin	Diketopiperazine	destruction of tumor blood supply network	Olga
Squalamine lactate	Aminosterioid	Competing with calcium-binding protein	Shark
Somocystinamide A	Lipopeptide	Activating caspases - apoptosis	Tawnykit
PG155	Poly peptide	Inhibition of angiogenesis	Shark
Granulatimide	Aromatic alkaloids	Cell cycle inhibition	Tawnykit
aeroplysinin-1	Alkaloid	Inhibition of angiogenesis	Sponge
Cryptophycins	Depsipeptide	Cell cycle inhibition and phosphorylation Bcl 2	Sponge
Caulerpenyne	Sesquiterpene	Inhibiting the formation of microtubules	Olga
Cycloprodigiosin hydrochloride	Alkaloid	Inhibition of NF-kB	Bacteria
Didemnin B	Depsipeptide	Induction of apoptosis through caspases	Tawnykit
Discodermolide	Polyketide	Acetylation and increasing cell death	Sponge
Fascaplysin	Alkaloid	Interfering with DNA structure	Sponge
Halichondrin B analogues	Macrolide derivative	Tubulin polymerization	Sponge
Alicylihalamide A	Macrolide	Inhibition of ATPase	Sponge

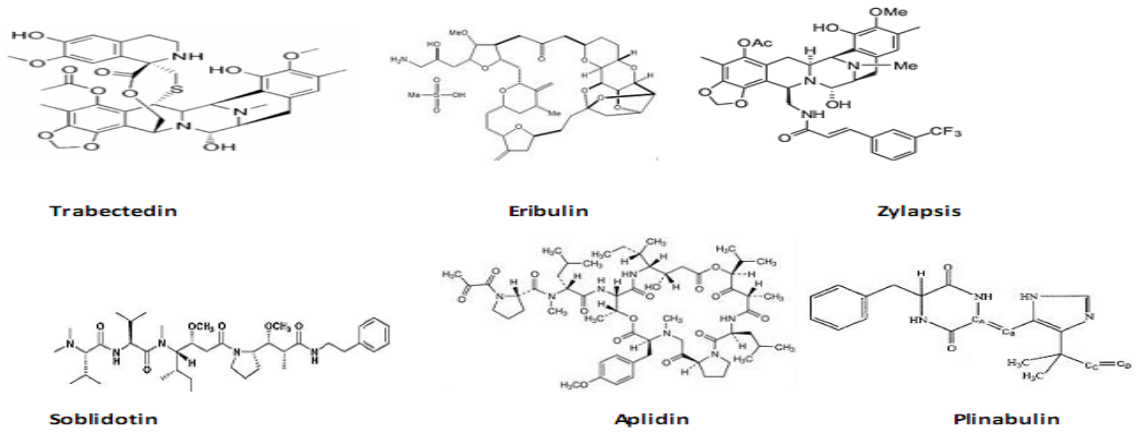

Figure 2: Chemical structure of a number of anti-cancer compounds extracted from water resources

Once bound, this reversible covalent adduct bends DNA toward the major groove, interferes directly with activated transcription, poisons the transcription-coupled nucleotide excision repair (TCR) complex, promotes degradation of RNA polymerase II, and generates DNA double-strand breaks (32,33).

Eribulin

Eribulin is an anticancer drug marketed by Eisai Co. under the trade name Halaven. It received permission to be used for the treatment of certain patients with breast cancer and liposarcoma in 2010 (34). Eribulin is a fully synthetic macrocyclic analogue of the marine natural product halichondrin B, the parent molecule being a potent naturally occurring mitotic inhibitor with a unique mechanism of action found in the Halichondria genus of sponges (35). Eribulin is a mechanistically unique inhibitor of microtubule dynamics, binding predominantly to a small number of high affinity sites at the plus ends of existing microtubules (36,37). Effectiveness of the drug is also being examined to treat other types of cancers, such as prostate and lung cancer (38).

Soblidotin

It is a compound of a synthetic peptide made by Symploca. In 2009, this compound entered phase III of clinical trials (39). Soblidotin is an inhibitor of angiogenesis (40). Soblidotin is one of the main factors in the growth and spread of tumors. The mechanism of action of many anti-cancer drugs is to prevent the blood network. Another function for this compound is to inhibit tubulin and avoid polymerization.

Aplidine

Plitidepsin (under the trade name Aplidin) is a chemical compound extracted from the ascidian Aplidium albicans. Plitidepsin is a cyclic depsipeptide, meaning it is a cyclic peptide in which there is one or more ester bond in place of one or more of a peptide bond (41). The compound is currently in Phase II of clinical trials. The effect of Aplidin on lymphoma and myeloma cancer cells has been proven (42). The cytotoxicity of this compound in concentrations is very low and such that IC50 is at the the nano-molar level. Aplidin causes cancer cell death by activating compounds involved in the apoptotic cascade (43).

Zalypsis

Zalypsis is a synthethic tetrahydroisoquinolone alkaloid, which is structurally similar to many marine organisms. The compound has been proposed as a potential chemotherapeutic agent in the treatment of solid human tumors and hematological malignancies. Zalypsis is a DNA binding agent, causing inhibition of the cell cycle and transcription, which can lead to double stranded DNA breaks (44,45). Studies have shown that this compound has an effect on breast cancer cells, prostate and urinary tract anti-cancer and has a small effect on colon cancer cells (46).

Plinabulin

Plinabulin was isolated from a marine alga associated Aspergillus CNC-139 and is being developed as an experimental cancer drug. It is a synthetic analog of the natural compound phenylahistin (47). Plinabulin interrupts tumor blood flow via disruption of the tumor's vascular endothelial cells resulting in tumor necrosis (46). It has undergone Phase I in 2006 and Phase II clinical trials for non-small cell lung cancer in 2009 (48).

Squalamine

Squalamine is an aminosterol compound with potent broad spectrum antimicrobial activity discovered in the tissues of the dogfish shark (Squalus acanthias) by a team led by Michael Zasloff in 1993. Squalamine was initially discovered on the basis of its anti-bacterial activity [49]. Squalamine is currently in a Phase II for the treatment of patients with lung cancer (50). In addition, the Phase II clinical trial of this compound is to treat ovarian cancer and prostate cancer (51).

Squalamine inhibit the growth of cancer cells through the inhibition of angiogenesis (52). The shelf-life of this compound is very short in the body so that its half-life in the bloodstream is about 7.5 hours, resulting in reducing side effects in humans. In spite of the low shelf-life in the bloodstream, stability within cancer cells is more than 5 days, resulting in increasing its influence on the cells.

There are 22 compounds of marine origin in different phases of clinical trials, including Tasidotin, Bryoststin, Marizomib, Hemiasterlin, and Elsudepsin. These compounds have been tested on a variety of cancer cells and have had good results (53-56).

Conclusion:

The seas and oceans are full of great resources that are still not well known. Diversity of conditions in the environment creates various mechanisms for nutrition, escape and defense, messaging and communication between different organisms. Inspired by these organisms, scientists are trying to find new substances and methods to improve human life. One of the main goals of the operation of sea creatures is to find new compounds for the treatment of diseases, especially cancer. Several compounds with anti-cancer properties have been isolated from sea creatures. After getting the necessary permits, some of which are manufactured and supplied in the pharmaceutical market of the world. The search for other compounds continues with the increasing growth in various parts of the world. Iran also has huge water resources including the Persian Gulf and Oman Sea in the south and the Caspian Sea in the north as well as a variety of lakes and rivers. There are a variety of organisms such as sponges and corals in the water that can be a good resource for extraction of medicinal compounds including the mentioned compounds in this study. Therefore, Iranian scientists and researchers can use this God-given wealth for production of the drugs needed for patients through a systematic planning.

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