Could marine life cure cancer? perspectives and challenges

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Abstract

Life started and evolved in water. Marine life is the key to the global function of the ecosystems and food chain. Could marine life also be the solution to human health problems, especially cancer? Marine life contains and produces a vast variety of substances that have beneficial properties for human health. Many of them can be used as functional food ingredients due to their antihypertensive, antioxidant, anti-microbial, anti-coagulant or anti-diabetic properties and many have the potential to be used as pharmaceuticals, especially for cancer, due to their antitumor properties. The recent advances in the analysis and identification methods of chemical substances in trace levels in the marine environment have provided the opportunity of better understanding of their formation mechanisms, fate and properties. Nowadays great research efforts are being devoted to the determination of their pharmacological potentials. Some of them are considered as prospective cancer therapeutics and have been subjected to clinical trials with promising results. The aim of this work is to review existing information on origin and properties of marine life substances with pharmaceutical action and the potential to be used as cancer therapy drugs. Recent results, analytical problems, future perspectives and challenges are discussed.

Keywords: marine life, natural pharmaceuticals, drugs, cancer, analytical methods

1. Introduction

Since ancient times people were looking for natural substances with therapeutic properties. Since life started in prehistorical oceans, there was more time for the adaptation and development of marine organisms (Fenical, 2006). Marine environment combines organisms and circumstances much different than the terrestrial environment, thus the bio-active metabolites isolated from the marine environment can have active groups rare or unknown to the terrestrial organisms (Bhakuni and Rawat, 2005). There is a large variety of bioactive substances produced by different marine organisms (Suffness and Pezzuto, 1990). However, only a limited number of marine organisms has been investigated regarding the bioactive substances produced and a very small percentage of these substances have been checked for their activity (Riguera, 1997). Difficulties to access them, as well as the complexity and high cost of the procedures for the isolation and separation of the substances are the main reasons for this (Martinez *et al*., 2013). The complexity of the analytical procedures involves the efforts to remove the inorganic salts from the extract, the prevention of growth of bacteria and fungi, and the effort to maintain the activity of the substance during water evaporation via freeze-drying procedures. Moreover, there is no uniform standardized technique for the separation of the contents of marine organisms extracts, therefore many procedures are based on trial-and-error (Mayer and Hamman, 2004, Mayer *et al*., 2010, Petit and Biard, 2013). The ultimate aim is the synthesis of the substance, and whenever this is not yet possible, the culture of the species from which the substance is isolated. In this way, higher amounts of the substance can be obtained, at lower cost. For the achievement of the synthesis of the active substance, its characterization is necessary, which is obtained via the determination of the structure of the nucleus, with the help of mass spectrometry data and libraries. Before the research for the synthesis of the substance or the culture of the organisms of interest can start, the activity as well as the toxicity of the substance needs to be tested. The activity of a substance is determined via comparison with a certified standard, or via the percentage of disease healing. The toxicity testing includes acute toxicity, lethal concentration and maximum tolerant dose, the reproductive and developmental effects. Finally, clinical trials are performed at human volunteers (Kerr and Kerr, 1999, Haefner, 2003, Martin, 2013). Marine environment still contains a vast range of substances many of which can act as potential anti-cancer pharmaceuticals; still waiting to be discovered/isolated. This field of research is very promising and particularly important for the health sector and human life, while the confrontation of analytical difficulties is a great challenge.

2. Characterization of active substances

The determination of the molecular structure of a natural product with high bio-active properties is very interesting and also very challenging. The knowledge of the biosynthesis of the secondary metabolites is very useful in order to determine the most possible substitutes since the nucleus structure is known. Spectral data such as infrared,

Table 1. Bioactive substances with anti-cancer action derived from marine organisms

Bioactive substance	Source (species)	PROPERTİES - USE
Laminarin	*Laminaria digitata*	Anti-cancer action, protection from radiation, reduction of cholesterol levels, wound healing, inflammatory. Immunomodulatory properties that increase resistance to bacteria, viruses and parasitic infection.
Fucoidan	Various Ochrophyta species such as species of genes *Fucus, Wakame, Hijiki*	Anti-cancer action, protection from radiation, reduction of cholesterol levels, wound healing, inflammatory. Immunomodulatory properties that increase resistance to bacteria, viruses and parasitic infection. Antithrombotic properties.
Salinosporamide A	*Salinispora tropica*	Anti-cancer drug in stage I of clinical trials. Strong action against multiple melanoma.
Thiocoraline	*Micromonospora marina*	Very cytotoxic against leukemia. Antibiotic action.
Carbenolide	*Amphidinium* spp.	*In vitro* cytotoxicity against human colon cancer cells.
Cephalostatin 1	*Cephalodiscus gilchristi*	Anti-leukemia metabolite.
Eleutherobin	*Eleutherobia* spp.	Anti-cancer action.
Sarcophinone	*Klyxum molle*	*In vitro* Anti-cancer action.
Aplyronine A	*Aplysia kurodai*	Anti-cancer action.
Aplysianin – A	*Aplysia kurodai*	Anti-cancer and antibacterial action.
CGX-1160	*Conus geographus*	Stage I clinical trials for the treatment of pain.
Dolastatin 10 (dolastatins)	Mollusks: *Dolabella auricularia* Bacteria: *Symploca* spp.	Anti-cancer substance in stage II of clinical trials.
Elisidepsin	*Elysia rufescens*	Stage II clinical trials with the name Irvalec^{R}, for its anti-cancer properties.
ES-287	*Mactromeris polynyma*	Stage I clinical trials for cancer.
Kahalaide F	*Elysia rufescens*	Stage II of clinical trials for its anti-cancer action particularly prostate, colon and lung cancer.
Kelletinin I & II	*Kelletia kelletti*	Inhibits growth of Bucillus subtilis and leukemic cells.
LU103793	*Dolabella auricularia*	Stage II of clinical trials for its cytotoxicity.
Peroniatriols	*Peronia peronii*	Antileukemic action.
PM1004	Nudibranchs	Stage II of clinical trials against cancer.

Sphinxolide	Not defined species	Anti-cancer action.
Porphyra	*Murex trunculus*	Traditional Chinese drug against leukemia (Danggui Longui) Anti-cancer properties.
Ziconotide, ω-conotoxins	*Conus geographus*	Action against heavy pain, epilepsy, and neurodegenerative diseases. Action levels 1,000 times higher than those of morphine for the treatment of some forms of pain. Clinically approved with the commercial name Prialt^{R}.
ACV1	*Conus victoriae*	Stage I clinical trials as analgesic substance.
Halovirs	*Scytalidium* spp.	Anti-cancer metabolite (particularly against prostate cancer). Anti-inflammatory and antivirus action (against herpes virus). No toxicity, no allergic reactions.
Gliovictin	*Asteromyces cruciatus*	Anti-cancer action.
Penochalasins D & H	*Penicillium* spp., Initially isolated from the alga *Ulva intestinalis*	Action against leukemia.
Plinabulin (NPI – 2358)	*Aspergillus ustus*	Stage II clinical trials for cancer.
Asperazine	*Aspergillus niger* This species has symbiotic relation with sponges of the gene *Hyrtios*	Cytotoxic against leukemia cells.
Ma'iliohydrin	*Laurencia* spp.	Anti-cancer action especially against breast cancer.
Aeroplysinin 1	*Aplysina aerophoba*	Anti-cancer properties against skin cancer.
Discodermolide	*Discodermia* spp. (e.g.. Discodermia dissoluta)	Stage I of clinical trials against cancer.
Gemcitabine	*Tectitethya crypta*	Against pancreas cancer, bladder cancer and lung cancer.
Geodiastatins	*Geodia mesotriaena*	Anti-leukemic action.
HTI 286	Semisynthetic derivative of Hemiasterlin	Stage I clinical trials for its anti-cancer properties.
Iasonolide	Sponge species	Anti-cancer action.
Icadamide A & B	*Leiosella* spp.	Anti-cancer action, antivirus and immunostimulatory action.
KRN-7000 (α-	*Agelas mauritiana*	Stage I clinical trials for its anti-cancer properties.

galactosycleramide)		
LAF389	*Jaspidae* spp.	Stage I clinical trials for its anti-cancer properties.
Laulimalide	*Cacospongia mycofijiensis*	Anti-cancer action *in vitro.*
Mycaperoxide B	*Mycale* spp.	Anti-cancer action.
Naamoidine A	*Leucetta chagosensis*	Treatment of skin and colon cancer.
Salicylihalamide A	*Haliclona* spp.	Anti-cancer action.
Spongidepsin	*Spongia* spp.	Anti-cancer action.
Stylostatin 2	*Stylotella* spp. *Phakellia costata*	Anti-cancer action.
Swinholide A	*Theonella swinhoei*	Anti-cancer action.
Thorectandrols A & B	*Thorectandra* spp.	Anti-cancer action.
Topsentins	*Topsentia gentrix*	Anti-cancer metabolite. Anti-inflammatory and antivirus action.
Zampanolide	*Fasciospongia rimosa*	Anti-cancer action.
Cytarabine ARA-C	*Cryptotythea crypta*	Anti-cancer and antivirus action. Approved after clinical trials. Commercial names: Cytosar-U^{R}, Depocyt^{R}.
Spongithymidine	*Cryptotethya crypta*	Anti-cancer action. Strong action against herpes virus and other viruses.
Spogouridine	*Cryptotethya crypta*	Anti-cancer action. Strong action against herpes virus and other viruses.
Alteramide A	Sponge: *Halichondria okadai* Bacteria: *Alteromonas* sp. (symbiosis)	Anti-cancer substance, strong action against leukemia, lymphoma and epidermal cancer cells.
Duryne	*Chribrohalina dura*	Anti-cancer action against colon, lung and breast cancer.
Dysideapalaunic acid	*Dysidea* spp.	If it proves to be non-toxic, it will be useful for treatment of diabetes.
E7389 (Eribulin Mesylate)	*Lissodendoryx* spp.	Stage III clinical trials for its anti-cancer properties against breast and lung cancer.
Halichondrin B	*Halichondria okadai*	Anti-cancer action.

		It has been isolated also from bacteria species (symbiosis)
Bryostatin 1	Bryozoans: *Bugula neritina* Bacteria: *Endobugula sertula*	Anti-cancer action. Treatment against leukemia, melanoma, ovary, breast and lung cancer. Stage II clinical trials.
Kahdehydrodidemnin B (APL)	*Aplidium albicans*	The drug name is Aplidine™ and has anti-cancer action. Stage II clinical trials. Reduces oxidative stress. Different action compared to known anti-cancer drugs.
Ascididemnin	*Leptoclinides* sp, *Didemnun* spp.	Anti-neoplasmatic substance, particular action against leukemia.
Namenamicin	*Polysyncraton lithostrotum*	Anti-cancer action.
Vitilevuamide	*Didemnum cuculliferum*, *Polysyncraton lithostrotum*	Anti-cancer action.
AE-941 (Neorastat)	Shark species.	Stage III clinical trials for anti-cancer action.
Didemnone C	*Didemnum voeltzkowi,* *Tridemnum cf. cyanophorum*	Anti-leukemic metabolite.
Ecteinascidins (Ecteinascidin-743, ET-743)	*Exteinascidia turbinate* (synthesized with zymosis of the bacteria *Pseudomonas fluorescens*)	Approved for anti-cancer action against breast and prostates cancer and against pediatric sarcoma with the commercial name Yondelis.
Granulatimide	*Didemnum granulatum*	Anti-cancer action

ultraviolet, mass spectra are obtained and compared to relevant libraries of similar compounds due to similar chemical or biosynthesis properties (Turabi, 2012). The bioactive substances isolated are not always new substances. Sometimes, substances already known are determined. The classical method of structural determination includes the fragmentation of the molecule in order to determine the nucleus, as well as several other transformation reactions combined to spectral analysis. X-ray crystallographic research is performed at the compound or at a heavy product that includes the atoms in order to determine the structure and stereochemistry of the substance (Fenical, 1997, Bhakuni and Rawat, 2005, Bak *et al*., 2011).

3. Origin/categories of substances

Table 1 summarizes the bioactive substances with anti-cancer activities that have been isolated from the marine environment, their origin and properties/use. According to the information reviewed, the majority of bioactive-substances origins from Porifera. This is attributed to the fact that Porifera as primary species had historically more time for adaptation and development, resulting in larger variety and activity of compounds produced. Most bioactive metabolites of this category have antibacterial, antivirus and anti-cancer action (Aneiros and Garateix, 2004). Next category according to the amounts of substances it produces is Mollusks, with a great range of various living conditions in different places, resulting again in many substances with anti-cancer action (Hamann and Scheuer, 1993). Chordates are the next source of anti-cancer action substances. The metabolite Aplidine, is of particular interest, due to its mechanism of action which is different from all anti-cancer drugs known up-to-date (Taraboletti, 2004). Most metabolites produced from Ochrophyta show anti-cancer action. Many of them have multiple therapeutic properties, such as Laminarin, with anti-cancer action, radiation protection action, cholesterol decreasing action, inflammatory action, immunological enhancing action. A very interesting category of substances is Toxins. They have intense toxicity, e.g. Tetradotoxin is 10.000 more toxic than CN. However in very small amounts they can act against pain, epilepsy, neurodegenerative diseases, and intense pain occurring at the final stages of cancer (Yashimoto and Murata, 1993, Llewellyn, 2006, Nishikawa, 2013).

4. Analytical problems

Although during the latest years there have been great developments in the sector of isolation and identification of substances from marine organisms' extracts for the identification of their bioactive characteristics, there is still no uniform standardized method for this procedure. This is due to the large diversity of marine organisms and therefore their bioactive metabolites, as well as due to differentiation of environmental conditions of life of the organisms and during sampling (Kijjoa and Sawangwong, 2004, Kim and Wijesekara, 2010). The most common procedure for the separation of the substance is column chromatography. Various types of this procedure are applied according to the purity of the substance. For example reversed phase column chromatography is very effective for most substances, but if it is not applied during the last steps of sample treatment (cleanup) it is possible that problems such as column deactivation occur (Meyer, 2010). There are particular problems occurring during screening of extracts from animals and plants. A major problem is that the active substance exists in raw extracts in very small concentration, resulting in the need of very high sensitivity techniques for its detection. In general, *in vitro* tests are more sensitive than the *in vivo* ones (Romano *et al*., 2013). Another problem is that the tests and methods used for the raw extracts must not be affected from substances that can cause "noise" at the results. Moreover they should not be affected from other existing compounds that could give a false positive result. The tests should be very selective. Of course all analytical methods should also have acceptable recovery, accuracy, repeatability, reproducibility and logical cost. (Teicher and Andrews, 2004, Bhakuni and Rawat, D. D., 2005)

5. Conclusions

The substances characterized by cytotoxic action and are tested with regard to their anti-cancer action are of particular scientific interest. Marine environment can provide a large variety and number of such compounds, contributing to the discovery of new drugs for cancer therapy. The fact that only a limited number of marine organisms have been studied for their potential to provide bioactive metabolites, while still from this limited number of organisms a large number of substances are already under clinical trials and several have been approved as anti-cancer pharmaceuticals, leads to the conclusion that the marine environment can indeed contribute to the development of health sciences, in particular towards therapy of cancer, through bioactive substances that are waiting to be discovered, and also through different mechanisms of actions of such substances.

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