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A REVIEW ON ANTICANCER AGENTS FROM MARINE SOURCES

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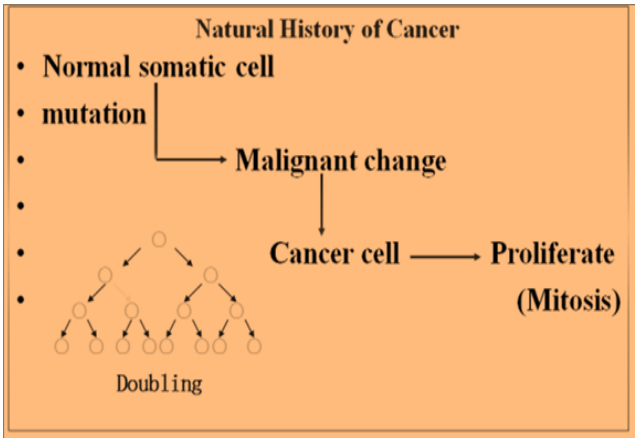
ABSTRACT

Cancer, known medically as a malignant neoplasm, is a broad group of various diseases, all involving unregulated cell growth. Unfortunately, despite the scientific substantiation and efficiency of the developed methods of treating cancer in preclinical studies, the expected success in clinical practice has not been achieved yet. Due to the shortcoming of chemotherapy, dose limits, side effects, and low selectivity for cancer cells, detection of much more efficient, harmless and highly selective antitumor drugs are required in urgent. So, now the research has been focused towards the development of novel anticancer drugs from the natural products. Nature has been instrumental as a source for therapeutics. Marine floras are extremely important oceanic resources, constituting over 90% of the oceanic biomass. They are taxonomically diverse, largely productive, biologically active, and chemically unique offering a great scope for discovery of new anticancer drugs. With the implementation of scuba diving tools and the development of sophisticated instruments for the isolation and elucidation of structures of natural products from marine organisms, major advances have been made in the discovery of marine derived therapeutics. Marine secondary metabolites are a promising source of unexploited drugs that have a wide structural diversity and have shown a variety of biological activities. These compounds are produced in response to the harsh and competitive conditions that occur in the marine environment. The compounds have displayed an array of pharmacological properties especially antioxidant, immune stimulatory, and antitumour activities. Due to the potential bioactivity of the natural products isolated marine microorganism, they represent a hopeful resource for discovering new anticancer drugs.

KEYWORDS: Anticancer, Marine Organisms.

INTRODUCTION TO CANCER

Cancer, known medically as a malignant neoplasm, is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous. Benign tumors do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body. There are over 200 different known cancers that afflict humans.[1]

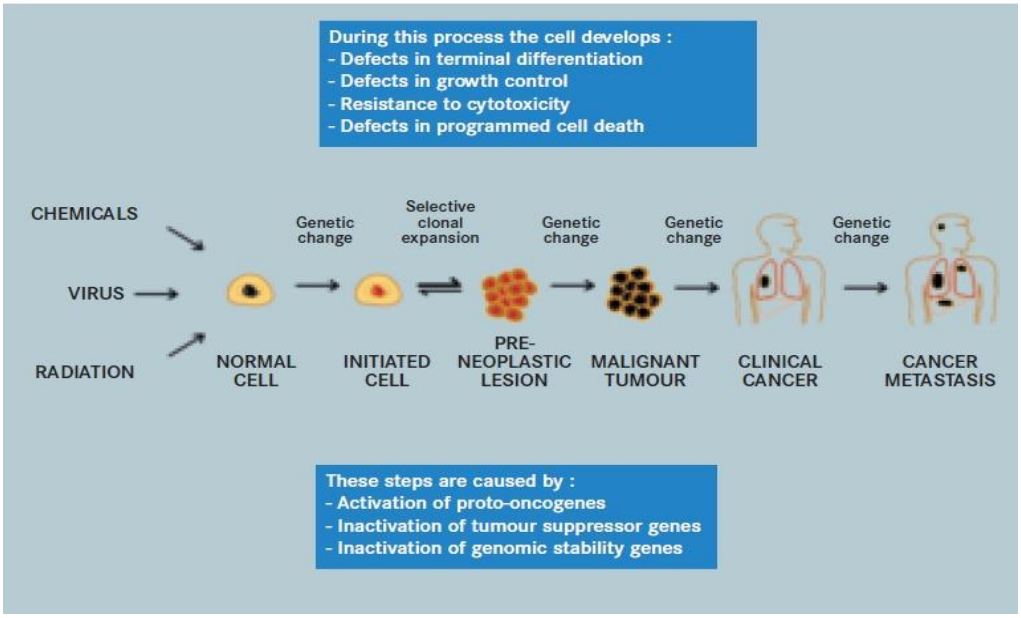


Mechanisms of tumor development[2]

The development of cancer may be initiated by environmental agents (chemical carcinogens, radiation, viruses) and inherited genetic factors (germline mutations).

Mutation of critical genes, including suppressor genes, oncogenes and genes involved in DNA repair, leads to genetic instability and progressive loss of differentiation. Tumors enlarge because cancer cells lack the ability to balance cell division by cell death (apoptosis) and by forming their own vascular system (angiogenesis). The transformed cells lose their ability to interact with each other and exhibit uncontrolled growth, invade neighbouring tissues and eventually spread through the blood stream or the lymphatic system to distant organs.

Tumors consist of cells whose growth and morphological characteristics are markedly different from those of normal cells. Criteria for malignancy include increased cell proliferation, loss of differentiation, infiltrative growth and metastasis to other organs.



Unfortunately, despite the scientific substantiation and efficiency of the developed methods of treating cancer in preclinical studies, the expected success in clinical practice has not been achieved yet, including the use of anti-cancer vaccines. All the cancer treatments are directed towards suppressing the various manifestations of the activity of cancer cells, so these treatments are symptomatic. Strictly speaking, according to the existing ideas about carcinogenesis, even modern standards of cancer treatment (surgery, chemotherapy, radiation therapy) are also symptomatic because they are only directed towards eliminating malignant tumor cells from the body, rather than at the mechanisms of their occurrence (DNA damage, etc.). One can say that the modern cancer treatment is the struggle with cancer cells, but not with the human disease. In the modern oncology the gap between scientific theory and clinical practice caused by the lack of understanding of the true pathogenesis of cancer is obvious.[3] Death due to cancer is the second highest amongst all diseases. Due to the shortcoming of chemotherapy, dose limits, side effects, and low selectivity for cancer cells, detection of much more efficient, harmless and highly selective antitumor drugs are required in urgent. So, now the research has been focused towards the development of novel anticancer drugs from the natural products. Marine microbes have gained enormous interest in the pharmaceutical community as they produce metabolites that are structurally unique and pharmacologically active. Due to the potential bioactivity of the natural products isolated marine microorganism, they represent a hopeful resource for discovering new anticancer drugs.[15]

Anti-Cancer Agents From Marine Sources

Sulfated O-polysaccharide with anticancer activity from the marine bacterium Poseidonocella sedimentorum KMM 9023T[4]

Several investigations have reported that sulfated carbohydrate polymers effectively inhibit proliferation and colony formation of cancer cells in vivo.(Fedorov, Ermakova, Zvyagintseva & Stonik, 2013). In this connection, the search and investigation of unique sulfated carbohydrate- containing biopolymers are becoming increasingly significant research topics. Gram-negative bacteria are an indispensable component of marine environment. Gram-negative bacteria are rich sources of structurally diverse substances with various biological and physiological activities. The most of Gram-negative bacteria produce lipopolysaccharides (LPS) on their outer membranes and their presence as a rule being required for survival and growth of the microorganisms. This is due to their role in the interplay with the external environment and host- bacterium interactions. Indeed, the molecular structure of LPS molecules is associated with the possibility of survival in marine habitats, protecting the cell from the destructive effect of natural stress factors. Recently it has been discovered and investigated several LPS with sulfated O- chains are produced by marine Gram-negative bacteria and demonstrated that sulfated OPS from *Cobetia litoralis* KMM 3880T and non-toxic *O*-deacylated LPS (DPS) from *Poseidonocella pacifica* KMM 9010T inhibit colony formation of various human cancer cells (Kokoulin et al., 2016; Kokoulin et al., 2017).

The study then was focused on the LPS which was isolated from one more marine bacterium of genus *Poseidonocella* – *P. sedimentorum* KMM 9023T (Romanenko, Tanaka, Svetashev & Kalinovskaya, 2012). Then structural study of the OPS and investigation of the anticancer activity of the DPS on human melanoma, colorectal carcinoma, and breast adenocarcinoma cells was carried on. The repeating unit of the OPS(O-specific polysacchrides) of *P. sedimentorum* KMM 9023T presents the disaccharide consists of 3-*O*-acetyl-2-*O*-sulfate-D-glucuronic acid and 3-deoxy-9- *O*methyl-D-*glycero*-D-*galacto*-non-2-ulosonic acid. The study provided another example of identification of Kdn as a component of cell wall polymers of Gram-negative bacteria the Kdn-containing OPS was found for the first time. Moreover, as far as we known, 9- *O*- methylderivative of Kdn was found for the first time. Previously, the presence of only 5-*O*-methyl- and4-*O*-methyl-derivatives had been reported (Gil-Serrano et al., 1998; Shashkov et al., 2012). In vitro investigation of anticancer activity. determination of the anticancer effects of DPS of *P.*

sedimentorum KMM 9023T was performed on human HT-29, SK-MEL-5 and MCF-7 cell lines.

Marine Bacteria

Secondary metabolites produced by marine bacteria have yielded pharmaceutical products such as novel anti-inflammatory agents (e.g., pseudopterosins, topsentins, scytonemin, and manoalide), anticancer agents (e.g., bryostatins, discodermolide, eleutherobin, and sarcodictyin), and antibiotics (e.g., marinone).

Evidence for the anti-tumor effect of L. acidophilus comes from studies conducted in their laboratory. Oral supplementation of the diet with viable L. acidophilus of human origin, which is bile resistant, caused a significant decline in three different faecal bacterial enzymes. The decline in faecal enzyme activity was noted in humans and rats. The bacterial enzymes that were affected included β-glucuronidase, azoreductase and nitroreductase. These enzymes catalyse the conversion of pro carcinogens to proximal carcinogens in the large bowel. These studies show that the addition of this strain of Lactobacillus to the diet can delay colon tumor formation by prolonging the induction of the latent period. These studies were extended in an animal model of colon cancer induced by the chemical carcinogen, 1,2-dimethylhydrazine (DMH). Suppression of β-glucuronidase enzyme might reduce DMH activation and subsequent tumor formation.[1] Kahalalide F (KF) is a depsipeptide isolated from the mollusk Elysia rubefescens from Hawaii and the compound is believed to be synthesized by microbes associated with the animal. KF induces cytotoxicity and blocks the cell cycle in G1 phase in a p53-independent manner. In vitro, KFdisplays activity against solid tumors with an interesting pattern of selectivity in prostate cancer cell lines. In addition, extensive invivo work demonstrates that the agent has activity in breast and colon cancers.[5]

Actinomycetes

Among the antibiotic-producing microbes, marine actinomycetes within the family Micromonosporaceae are very promising. These microbes are found to be a potent sources of anticancer agents that target proteasome function and their industrial potential is validated by several pharmaceuticals.

Thiocoraline is a novel bioactive depsipeptide isolated from Micromonospora marina, a marine microorganism that inhibits RNA synthesis. The bioactive compound is also

selectively cytotoxic against lung and colon cancer cell lines as well as melanoma and it exerts preferential antiproliferative effects in colon cancer cell lines with defective p53 systems.[6]

Micro Algae. Marine blue-green algae (Cyanobacteria)

Some of themarine cyanobacteria appear to be potential sources for large-scale production of vitamins (B complex, E) of commercial interest. Scytonemin is a protein serine/threonine kinase inhibitor, isolated from the cyanobacterium Stigonema sp. and this compound is a yellow-green ultraviolet sunscreen pigment, known to be present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae. Scytonemin regulates mitotic spindle formation as well as enzyme kinases involved in cell cycle control and the compound also inhibits proliferation of human fibroblasts and endothelial cells. Thus scytonemin may provide an excellent drug as protein kinase inhibitors to have antiproliferative and anti-inflammatory activities.[7]

Marine algae (Cyanophyceae)

Cyanobacteria in general and marine forms in particular are rich sources of novel bioactive compounds (including toxins) for pharmaceutical applications. scytonemin, isolated from Stigonema sp., is a protein serine/threonine kinase inhibitor. It is yellow-green ultraviolet sunscreen pigment present in the extracellular sheaths of different genera of aquatic and terrestrial blue-green algae. Scytonemin regulates mitotic spindle formation as well as enzyme kinesis involved in cell cycle control. Furthermore, the compound inhibits proliferation of human fibroblasts. and endothelial cells. Thus, scytonemin may provide an excellent drug, as protein kinase inhibitors do have antiproliferative and anti- infl ammatory activities.[8]

Anchovy

Peptide fractions showing anticancer activity were isolated from anchovy sauce, and their abilities to induce apoptosis in a human lymphoma cell (U937) were determined. The desalted hydrophobic peptide fraction separated from anchovy sauce was found to possess strong antiproliferative activity against U937 by inducing apoptosis which was accompanied by an increase of caspase-3 and -8 activities.[9]

Eel

Kwak et al. reported a growth inhibitory activity of the eel skin mucus (ESM), from A. japonica from Korea, on human leukemia K562 cells, by causing apoptosis. They conducted immunoblotting analysis which suggested that extracellular signal-regulated kinase 1 and 2 (ERK1/2) and p38 signals could be involved in the ESM mediated-apoptosis.[10]

Mussel

Beaulieu et al. have obtained hydrolysates of whole blue mussels by a commercial *Bacillus* protease complex with broad specificity to hydrophobic amino acids (Protamex). Then fractionated it based on molecular mass then tested it for anti proliferative activity against four immortalized cell lines, namely A549 (type II pulmonary epithelial cells), HCT15 (colon carcinoma cells), BT549 (breast carcinoma cells), and PC3 (prostate cancer cells).

They have found that only the 50 kDa hydrolysate fraction, enriched in peptides, possessed antiproliferative properties with all tested cell lines, exhibiting high activity towards prostate cancer cells and type 2 pulmonary epithelial cell lines.[11]

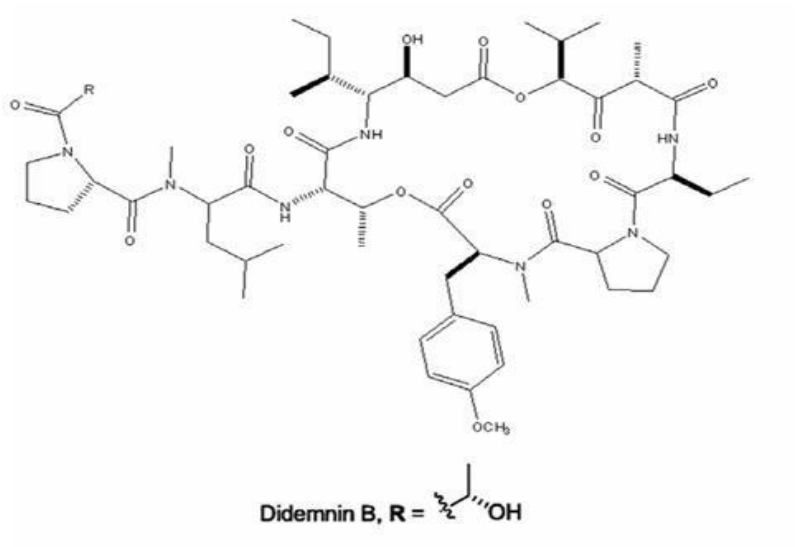
Sea cucumber

The triterpene glycosides were found to possess a wide range of pharmacological activities, including cytotoxic activity. frondoside A (5)is a triterpene glycoside which can be isolated from the edible Atlantic sea cucumber Cucumaria frondosa. They have found also that frondanol A5 reduced azoxymethane-induced colonic total ACFs and multicrypt ACFs in a dose-dependent manner. Moreover, treatment with frondanol A5, at 450 ppm concentration, also caused an appreciable increase (66%) in the p21-positive cells and substantial decrease (46%) of proliferating cell nuclear antigen (PCNA)-positive cells in the ACFs compared with the azoxymethane-treated control diet.[12] [13]

It was concluded that frondanol A5 mediates G2 arrest and not mitotic arrest. Recently, the same group has investigated the capacity of frondanol A5 in enhancing innate immune responses as well as in inhibiting intestinal tumor in APC Min/+ mice. They have found that frondanol A5 caused a decrease of small intestinal polyps (SIP) and colon tumors (CT) in both male and female mice.[14]

Sea-squirt

Didemnins are cyclic depsipeptide compounds that were isolated from a tunicate sea-squirt of the genus *Tridemnum* belonging to family Didemnidæ. They were collected in the Caribbean Sea in 1978. More than nine didemnins (Didemnins A-E, G, X and Y) have been isolated from the extract of *Tridemnum solidum*, Didemnin B is the one that possesses the most potent biological activities. Mechanistically, didemnin B acts at the GTP-binding protein elongation factor.[16]



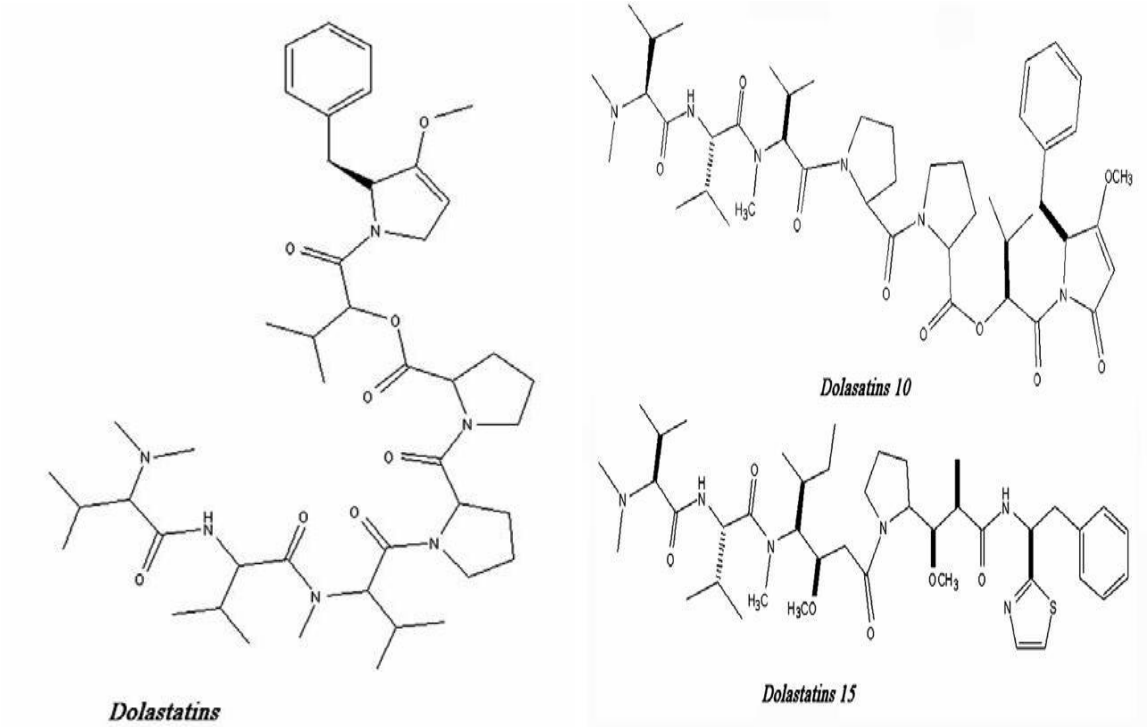
Sea hare

Dolastatins are peptides isolated from the Indian Ocean sea hare, *Dolabella auricularia*. Among the dolastatin family, the linear peptide dolastatin 10 and the desipeptide dolastatin 15 exhibit the most promising anti proliferative actions.[17]

Dolastatins 10 and 15 are small peptides; Dolastatin 10 is a pentapeptide with four of the residues being structurally unique (dolavaline, dolaisoleucine, dolaproline, and dolaphenine, in addition to valine).It was selected for Phase I clinical trials as anticancer agent for use in the treatment of breast and liver cancers, solid tumours and leukemia.[18]

Dolastatin 10 was selected for clinical trials because of its more favourable preclinical profile.[19] It inhibits microtubule assembly, causing cells to accumulate in metaphase and is extremely potent *in vitro* but it caused bone-marrow toxicity in initial clinical trialsand local irritation at the injection site and mild peripheral neuropathy.[20]

Dolastatin 15, a seven-subunit depsipeptide derived from Dolabella auricularia, is a potent antimitotic agent structurally similar to dolastatin 10, a five-subunit peptide isolated from extracts of the Indian Ocean sea hare **D. auricularia**. Indeed, numerous dolastatin 15-related peptides have been isolated from diverse marine cyanobacteria. Its linear depsipeptide sequence is composed of seven amino acid or hydroxyl acid residues.[21]



Marine Mollusk

Kahalalide F (KF) belonging to the family of dehydroaminobutyric acid-containing peptides derived from the marine mollusc Elysia rufescens found in Hawaii. The structure of KF contains a lateral chain and a cycled region with the molecular formula C75H124N14O16. KF is the largest and most active of the seven natural compounds isolated from *E. rufescens.* KF displays both *in vitro* and *in vivo* antitumor activity in various solid tumor models, including colon, breast, non–small cell lung, and in particular prostate cancer.[22]

In certain experimental systems to perform the studies to determine the mechanism of action of Kahalaide F showed that, it caused a disruption of lysosomal membranes and consequently the formation of large vacuoles. This mechanism is unique among anticancer agents. This may also cause increase in acidification of the intra-cellular space which is a stimulatory event that initiates a pathway for apoptosis.[23]

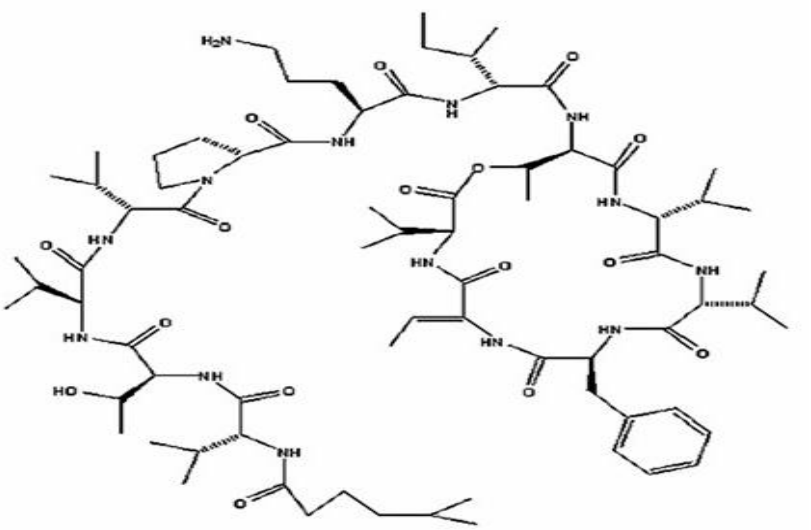


Fig. 4–Chemical structure of khalalide F

CONCLUSION

Various synthetic anticancer drugs have harmful side effects on human beings. Natural compounds play important role to prevent cancer. Among various natural sources, the marine sources are least explored for anticancer activity and they deserve special attention. Marine organisms produce variety of bioactive compounds which have unique structures that possess potential medicinal values. Marine secondary metabolites are a promising source of unexploited drugs that have a wide structural diversity and have shown a variety of biological activities.

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