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Marine Antineoplastic Templates: Clinical Trials (I-III) and Motifs Carried *via* Antibodies to Target Specific Cancerous Tissues

Abdel-Nasser El-Shorbagi[1]*, Sachin Chaudhary[1], Anurag Chaudhary[2], Garima Agarwal[2], Prabhash Nath Tripathi[2], Shweta Dumoga[2], Alaa Ali Aljarad[1], Esraa Omer[1], Fatma Mahmoud[1], Ramesh Kumar Gupta[3] and Mahmoud Hamed Mohamed[4]

[1]Department of Medicinal Chemistry, College of Pharmacy, University of Sharjah, Sharjah, United Arab Emirates.
[2]Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, NH-58, Baghpat Road Crossing, Bypass Road, Meerut, India.
[3]Department of Pharmacology, Hygia Institute of Pharmaceutical Education and Research Lucknow, Uttar Pradesh, India.
[4]Department of Pharmacognosy, College of Clinical Pharmacy, Albaha University, Saudi Arabia.
*Corresponding author Email: aelshorbagi@sharjah.ac.ae_

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Aquatic environment is one of the important sources of active agents that own diverse biological properties. Metabolites from these sources are considered as alternate source to meet the mandate for effective medicines. Despite notable developments in cancer managing and/or treatment in the past years, there remains a vital requirement for innovative agents and/or innovating approaches to treat resistant and solid tumours. However, in the recent era there are new technological innovations in the elucidation of the structures, the semi-synthetic and synthetic approaches of the new antineoplastic compounds. Biological assays enable isolation and clinical evaluation of numerous scaffolds from the marine environment. This review gives a general summary of some anti-cancer agents with a brief description of their mechanisms of action. It sheds a view to the approved drugs, the potent scaffolds that newly modulated as antibody-drug conjugates, and the drug-candidates under clinical phases (I-III) with their status.

Keywords: Antibody drug conjugate, Anticancer agents, Clinical phase, Marine drugs, Metabolites.

Cancer conclusively, is the disease resulted as a reflection of cell's overgrowth and uncontrollable proliferation. It is among the pre-eminent cause of morbidity and mortality in the world.[1-2] Cancer has risk factors that predispose patients to it and these factors could be either internal or external. Internal factors are those related to patient immunity or genetic mutations. External factors include aging, obesity, smoking, lack of physical activity and exercise and exposure to infecting substances or hazardous substances.[4] Cancer can be more complicated when cancer-cells start invading to the surrounding local environment in the body by metastasis that is responsible for 90% of deaths in cancer patients.[3-5]

Cancers can be detected early or later and sometimes accidentally with patients being treated or diagnosed for other types of diseases. [6-8] The diagnosis of cancer can be carried out based on the symptoms, tumour markers or histopathological tests that can be combined with other approaches like imaging techniques.[9]

Cancer management may be approached by one of the three methods such as surgery, radiation and chemotherapy or a combination of two of them.[10] The problems associated with these approaches include the side effects that will affect the normal cells and lead to a decreased patients life quality.[11] Other problem is that the treatment may not be useful as a result of tumour metastasis or drug resistance.[12]

Cancer is still a major public health problem that requires establishment of new strategies to discover new drugs that are able to fight it.[1] The drugs obtained from natural origin can be formulated in three structural forms: original, semisynthetic or analogue structures. Recently, the interest has been driven towards marine as a source of natural products mainly due to the structural diversity and availability of multiple scaffolds that can serve in the field of therapeutics as lead compounds, in particular, secondary metabolites that are produced by different aquatic organisms.[1,13]

Metabolites produced during the life of organisms are assumed as a defensive mechanism for survival and adaptation with life surroundings. Beside the so many scaffolds reported for anticancer activity, marine-secondary metabolites representing an important addition. In this review, the light is focused on the diverse secondary metabolites, and it will provide an explanation of their value as anticancer compounds. Previously, we reported several frames including natural, semisynthetic, and synthetic anticancer agents.[14-20] This review is a valuable contribution to look for other structural templates of promising new antineoplastic agents to treat resistant and solid cancers.[21-27]

Aquatic Sources as Anticancer Agent

Thousands of secondary metabolites had been isolated from different sea creatures such as *plants*, *macroalgae* (seaweed), *microalgae*, *bacteria*, *actinomycetes*, *fungi*, *sponges* and *soft corals* all are viewed in the area of medicinal field.[4] Aquatic plants live in a harsh climate. One of the most recognized plants providing anticancer agents is *mangrove* that produces bioactive compounds and secondary metabolites like hormones and anticancer agents.[28] Table 1, illustrated the summary of approved anticancer agents and drugs under clinical trials.

Aquatic Bacterial Metabolites

Pseudomonas provided metabolites that are active against microbes while others bearing cytotoxic activity e.g. dibutyl-phthalate and di-(2-ethylhexyl)phthalate (compound 1, 2, Table 2) are reported as Cathepsin B inhibitors.[29-30] The other types of aquatic bacterial-metabolites from *Lactobacilli* and *Noctiluca scintillans* represented anti-proliferative eûects toward colon and melanoma cancer.[31-33]

Gram-Positive Mycelial Bacteria

Actinomycetes produce metabolites to highest extent that is why they account about 45% of total marine metabolites. The highly potent thicoraline and BE-22179 (Compounds 3, 4, Table 2), representing a large 26-membered polypeptide ring with SS-bond and hydroxyl-quinolone moieties, and enterochelin (Compound 5, Table 2) as three 2, 3- dihydroxybenzamides in 12-memered cyclic structure,[34] isolated from *actinomycin* called *Micromonospora marina*. They are potent cytotoxic compounds that are effective against colon cancer.

Sponges Provided Pentacyclic-22-Membered-Ring Scaffold

These are of high contribution by ~ 30% of all-natural products of marine origin and of important biological activities.[35] The moderately active cytotoxins spongo-thymidine and spongo-uridine were isolated from *Caribbean* sponge t*ethya crypta.*[4] Eribulin (Compound 6, Table 3) which is a semisynthetic analogue of halichondrin B (Compound 7, Table 2) of IC50 = 7 uM had been isolated from sponge *Halichondria okadai*. Compound 6; a perhydro-pentacyclic-structure in a 22-membered-ring in the smaller frame of macrocycle. It provided potent IC50 value of 0.27 nM, was developed as mesylate (methansulfonate) salt. It stopped and emphatically hindered the development rate of microtubules.[36-39] had been obtained from sponge *Halichondria okadai*. It also, provided anticancer activity against breast cancer.[39] Eribulin has antimitotic and non-mitotic effects. It hinders microtubule polymerization

interfering with microtubule-dynamic-stability as an antimitotic. While the non-mitotic action on tumour biology have moreover been built up. It counts for tumour vasculature remodelling, expanded vascular perfusion, decreased hypoxia, and phenotypic changes.[40] Tubulin displayed antiproliferative action against many diverse human cancer cell lines. Eribulin decreased both the rate and degree of tubulin polymerization, also it affects more than one stage in cell-cycle like G2 and M in lymphoma and pancreatic cancer cells and also it leads to initiation to apoptosis after 8-10 hrs.[40-41] Eribulin has high affinity to microtubules. In non-mitotic mechanism Eribulin has three different mechanisms, one is through its impact on tumor vascular remodelling and perfusion, another is through its effects on EMT (epithelial mesenchymal transition) process, and finally its effects on the relocation, assault and metamorphosis of cancer cells.[42]

Fungal Sources Provided Indole-Bearing Pentacyclic Angular Scaffold

Some of fungi secondary metabolites have antioxidant activity toward free radical. Fungal xanthone derivatives produced by several numbers of plant families and fungi, *Penicillium raistrickii*, many *Phomopsis* spp. Alkaloids separated from *Penicillium* spp., found in deep ocean showed antitumor activity. These alkaloids are meleagrin analogues, meleagrin D (Compound 8, Table 2) and diketo-piperazine, roquefortine (Compound 9, Table 2) induced HL- 60 cell death or detained the cellular process through G_2/M phase, and bearing mild cytotoxic activity (against A-549, IC50 of 32.2 and 55.9 μM, respectively.[4, 43].

Soft Corals Provided 14-Membered-Carbocyclic Scaffold

Sarcophyton is widely spread in tropical and sub-tropical oceans. One of the important metabolites produced by soft coral is cembranoids like cembranoid diterpine (Compound 10, Table 2). Cembranoids have a verity of activities, like cytotoxic and anti-inflammatory. It is reported that furano-cembranoids from *Nephthea spp*, and *Sarcophyton cherbonnieri* are effective against breast cancer and liver cancer.[1, 4] The secondary metabolites are structurally variable and possessing valuable biological activities.[44] The utmost familiar domains are carbohydrates (glycosides, polysaccharides), peptides, alkaloids, polyketides, terpenes, and polyphenols.[1, 4]

The followings are brief explanations of each class:

Polyketides Scaffolds are large groups of secondary metabolites that contain alternating carbonyl and methylene groups, they include macrolides, polyethers, polyols and aromatics.[1]

Polyphenols scaffolds, also named polyhydroxyphenols.[45] are natural products that have phenolic skeleton and they are divided into subgroups according to either their structure, function or origin. These subgroups are: phenolic acids, poly phenolic flavonoids, tannins, catechin, anthocyanidins, epigallocatechin, lignin, epigallocatechin gallate (Compound 11, Table 2), [46] and gallic acid (Compound 12, Table 2).[47-49]

Terpenes scaffolds are secondary metabolites of isoprene units. Terpenes of different scaffolds of different numbers of carbons as C-10, C-15, C-20, C-25, C-30 and C-40[58] have been reported as more powerful antibacterial than being cytoxic.[59-60]

Alkaloids from sea sources as nitrogen-containing natural scaffolds are many subclasses such as indole, pyrrole, pyridoacrine, isoquinoline, guanidine or amino-imidazole.[58-60]

Peptides Scaffolds having many physiological effects in the cells obtained by extraction from sea sources. Peptides are isolated by enzymatic hydrolysis of organism-proteins.[61]

Carbohydrates $(CH_2O)_n$ of sea sources are involved in glycoproteins, lipids and with RNA and DNA. Mono-saccharides, di-saccharides and poly-saccharides were identified.[47] The most common class of carbohydrates are the polysaccharides. Some of the polysaccharides have potent anticancer effects via interfering with DNA synthesis, induction of apoptosis and other mechanisms of actions.[1, 47, 61]

All of the aforementioned bioactive classes had been obtained from different sea-sources like: sponges, molluscs, tunicates, corals, ascidians, bacteria, fungi, sea weed. [1, 48] They are active against many types of cancer and exhibited anti-cancer activity via cell growth inhibition, disruption of the mitotic spindle, induction of apoptosis and inhibition of invasion or metastasis.[1]

Approved Anticancer Marine Drugs

Secondary metabolites were studied broadly throughout the last 30 years for their

biological activities.[62] Cytarabine, brentuximab vedotin, eribulin mesylate, and trabectedin are some of the approved anticancer agents.

The followings are the approved anticancer agents.

Cytarabine

Food and drug administration (FDA) approved cytarabine in 1969. It is now a synthetic nucleoside anticancer drug that has been originally obtained from sea *Cryptotheca crypta* sponge.[1] There are other trivial names for cytarabine including chemical name, Ara-C and cytosine arabinoside.[63] Cytarabine (Compound 16 , Table 3) acts in phase S-specific manner to induce cytotoxicity and kill cancer cells through inhibition of DNA polymerase and being incorporated into DNA instead of the normal DNA building blocks.[63] Cytarabine is indicated for the treatment of leukaemia, [1, 63-64] described by the reproduction of immature leukemic blasts and their invasion to the bone marrow. It can be caused by intrinsic (genetic) or extrinsic (inflammation and release of cytokines and chemokines) factors.[66] It is administrated by intravenous infusion, intramuscular, intrathecal or subcutaneous injections.[67] Biologically it must be activated by phosphorylation when it is up-taken by the cells to the active form cytarabine-triphosphate to be able to induce its effect.[63] It is metabolized by being deactivated via deamination into the inactive and non-toxic form uracil-arabinoside and this metabolism decreases its activity [63-64].

One approach used to solve the issue of deamination and inactivation of cytarabine was to co-administer it with tetrahydro-uridine which is a potent inhibitor of cytidine deaminase so the antitumor activity of cytarabine will increase.[64]

Because of its short half-life it is advised to overcome this problem via prolonged infusion of cytarabine in a high-dose therapy which will lead to increased levels in the cerebrospinal fluid where cytidine enzyme is absent and the drug can remain active to induce its effect.[66-67]

Targeting of folate receptor by designing the prodrug of cytarabine solved the problem of its high hydrophilicity. This prodrug was assembled (Figure 1) to form spherical nano-assemblies (bare NAs) that adsorb folic acid-bovine serum albumin conjugate and (NAs/FA-BSA) form folate receptor targeting molecule. The conjugate concentrates in cancer cells that have increased expression of folate receptor therefore the antitumor activity of cytarabine will increase.[68]

Trabectedin

Trabectedin (Compound 17, Table 3) is an alkaloid from *Ecteinascidia turbinate.* It was approved by *European medicines agency* (EMA) in 2007 as a single medication for the treatment of rare solid tumours of mesenchymal cells.[65] It is the foremost marketed natural medicine for relapsed ovarian cancer. Recently, trabectedin was accepted by FDA in 2015.[69]

The results of ten years of use have shown a suitable toxicity proûle, without evidence of accumulative side eûects. However, because of an intensive hepatic metabolism liver dysfunction, predominantly chartered by increased transaminase levels, was reported as frequent side eûect.[66-72]

Trabectedin collaborate with DNA double helix, the structure of the compound triggers a cascade of occasions that restricted with a few translation components. It also causes inflection of cytokines and chemokines by typical cells.[73]

The preclinical studies on combination of trabectedin with other anticancer drugs have been currently progressing globally and one of the combinations including (trabectedin-pegylated-liposomal doxorubicin) was authorized by the European commission for treating relapsed platinum-sensitive ovarian cancer.[73, 4]

Antibody drug conjugates (ADC)

Brentuximab Vedotin (Adcetris™)

Brentuximab Vedotin (Compound 18, Figure 2) is one of the recent medications successfully endorsed by FDA in 2011 and received a conditional approval from EMA in 2012 for Hodgkin and non-Hodgkin lymphoma treatment. Brentuximab vedotin represents the novel strategy of targeting drugs. It is CD-30 directed antibody-drug conjugate (ADC) containing three major fragments: a chimeric human-murine IgG1 that selectively targets CD30, monomethyl auristatin E; MMAE (Compound 15, Table 2), related to dolastatins such as dolastatin 10 and 15 (Compounds 13 and 14, Table 2).[74-75] MMAE is a fully synthetic analogue of dolastatin 10, isolated *Dolabella auricularia*. Later scientists isolated dolastatins from cyanobacteria *Symploca hydnoides* and *Lyngbya majuscule* which are a part

of the sea hare's diet. To date, dolastatin 10 is the most powerful antineoplastic substances known, with an ED_{50} in the picomolar range against various cancer-cell lines. Dolastatins *in-vivo* activity is not adequate for direct application as antineoplastic drug. Phase I and phase II clinical trials of dolastatin 10 and the water-soluble analogue auristatin PE results indicated that they were ineffective due to lack of efficacy and existence of side effects. In this strategy MMAE is linked to a protein that targets CD30 (a cell membrane protein sitting on the surface of Hodgkin's lymphoma cells). This linkage has resulted in highly effective and well tolerated agent, Brentuximab-vedotin. It took about 40 years from the initial bioactive extract to the approved drug.[76-77]

Pinatuzumab Vedotin

Pinatuzumab Vedotin (Compound 19, Figure 2) is another ADC is aimed to act against surface antigens associated with cancer. It is consisting of an anti-microtubule MMAE attached to another protein anti-CD22 antibody through peptide linker that can be cleaved by protease enzyme. CD22 is one of the immunoglobulin superfamily, restricted to and expressed by mature B-lymphocytes. CD22 has a critical role in regulation of B-lymphocytes mediated signalling and it also regulates the function and survival of B-lymphocytes as well as apoptosis.[74-78] The mechanism of action is when Pinatuzumab Vedotin binds to CD22, it gets into the cell then it will start releasing its cytotoxic agent MMAE that will act against microtubules in a way similar to vincristine mechanism (microtubules destabilisation).[74-78] Phase I trials suggested that PV can be given alone or in combination with rituxiamb to treat refractory NHL or CLL.[75-78]

The advantages of using Pinatuzumab Vedotin include site specific drug delivery, increased efficacy and reduced systemic side effects. Subsequently, phase II trials started by *i.v*. dosage of 1.8 mg/kg, body weight or more given in a cycle of 21 days.[75-79] The toxicities that were recorded with Pinatuzumab Vedotin include non-hematological toxicity (nausea, diarrhea, fatigu), grade-3 neutropenia, thrombocytopenia and peripheral neuropathy. Most side effects can be reduced by extending the cycle length to 28 days and giving growth factors that allow neutrophils to become healthy and return to the normal count more quickly [75-80].

Glembatumumab Vedotin

Glembatumumab Vedotin (Compound 20, Figure 2) is right now in clinical trial phase-2 for treating osteosarcoma, melanoma, and breast cancer. It is an antibody-drug conjugate (ADC) that targets glycoprotein GPNMB (Glycoprotein Nonmetastatic Melanoma Protein B). GPNMB is involved in multiple functions, examples are its anti-inflammatory effect, role in mineralization of bone and differentiation of osteoblasts. It also functions in cellular adhesion and gets localized exactly in plasma membrane[81-82].

GPNMB is highly expressed in a very wide group of cancers including glioblastoma, astrocytoma, breast cancer, gastric cancer, and lung cancer. GPNMB is a glycoprotein comprises a huge extracellular space with cytoplasmic tail composed of short 53 amino acids. GPNMB expression is regulated by various cytokines, growth factors, microRNAs (miRNAs) and by protein stabilization. GPNMB is involved with varied patterns in a wide range of tissues including bones, skin, liver, and immune system.[83-87] The role of GPNMB in tumour formation is in melanoma, GPNMB is present in both cancer cells and normal cells but its percentage in cancer cell is higher (60%-80%) while in normal cell is (50%). For growth and metastasise, melanoma needs GPNMB, a specific phonotype of GPNMB is needed as knockdown the glycoprotein in some immune-competent mice that have melanoma studies found that no change in their growth, compared to culturing of t-cells with GPNMB. Knockdown causes the T-cell ability of functioning is impaired, it affects the production of inflammatory markers like IL-2 and IFN-ã and lose of ability to detect and kill the target cell. Glembatumumab Vedotin is a monoclonal antibody that mainly targeting GPNMB, in a recent study, the activity of Glembatumumab Vedotin was tested in number of osteosarcomas as a result, 85% of the cells responded to the drug. As shown in (Figure 2) GPNMB has multiple critical functions in cancer cells formation and if inhibited by Glembatumumab Vedotin, cancer can be treated.[88-90]

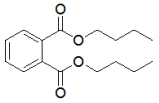
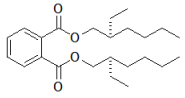
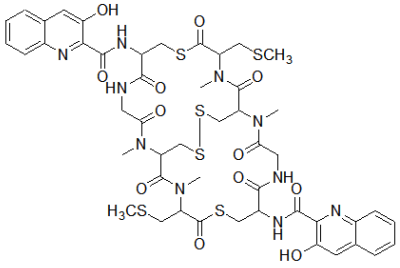
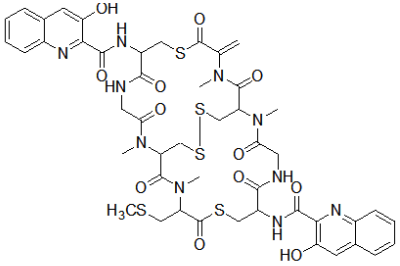
Tisotumab Vedotin

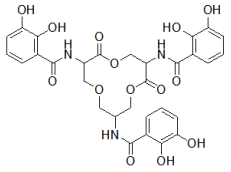
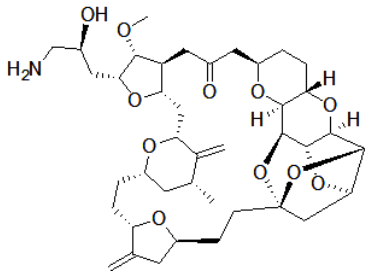
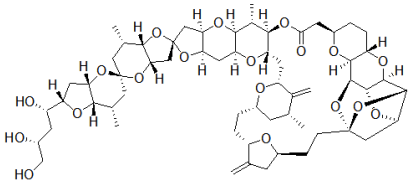
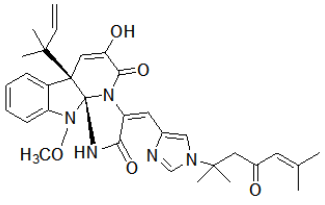
Tisotumab Vedotin (Compound 21, Figure 2) is also an ADC that can be isolated from marine

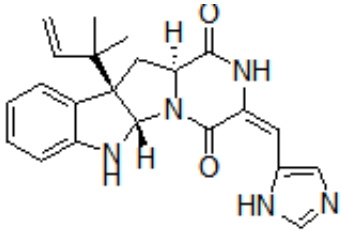
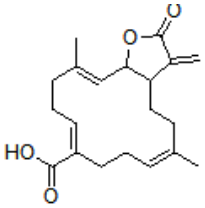
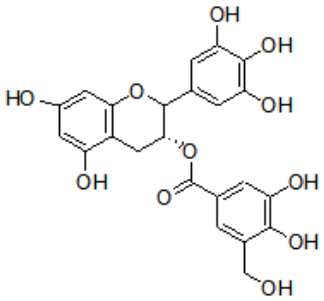
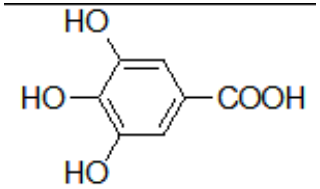
Table 1. Summary of approved anticancer agents and drugs under clinical trials

Compound	Approval year or clinical trial phase	Chemical class	Marine origin	Cancer type targeted	Mechanism of action
Cytarabine	Approved by FDA in 1969	Nucleoside	Sponge	Leukemia	Anti-metabolite
Trabectedin	Approved by EMA and FDA in 2007 and 2015 respectively	alkaloid	Tunicate	Ovarian cancer	Growth inhibition
Eribulin mesylate	Approved by FDA in 2016	Macrocyclic ketone	Sponge	Lymphoma, breast, and pancreatic cancers	Antimitotic
Brentuximab Vedotin	Approved by FDA and EMA in 2011	Antibody-drug conjugate (ADC)	Mollusk	Hodgkin and large cell lymphoma	CD30 directed ADC
Bryostatin 1	Phase I clinical trials	Macro-cyclic lactone	Bryozoa, Sponge, Tunicate	Lymphoma	PCK inhibitor
Hemiasterlin (E7974) and Taltobulin (HTI-286)	Phase I clinical trials	Tripeptide	Sponge	Colon, breast, ovary, and lung cancers	Antimitotic(Micro-tubules de-polymer-isation)
Pinatuzumab Vedotin	Phase I clinical trials	ADC	Mollusk, cyano-bacteria	Non-Hodgkin lymphoma and chronic lymphocytic leukemia	Microtubules de-polymerisation
Tisotumab Vedotin	Phase I clinical trials	ADC	Mollusk, cyano-bacteria	Prostate, pancreatic, and cervical cancers	Microtubules de-polymerisation
LAF389	Phase I clinical trials	Peptide	Sponge	Various types of cancer	Methionine aminopeptidase inhibitor
Tasidotin	Phase II clinical trials	Peptide	Cyano-bacteria	Various types of cancer	Micro-tubules depolymerisation
Glembatumumab Vedotin	Phase II clinical trials	ADC	Mollusk	Melanoma, osteosarcoma, and breast cancer	Inhibition of transmembrane GPNMB
Discodermolide	Phase I/II clinical trials	Polyketide	Sponge	Breast, ovarian and lung cancers	Microtubules polymerisation
Soblidotin	Phase I/II clinical trials	Peptide	Bacteria	Advanced and metastatic non-small cell lung cancer	Microtubules depolymerisation
Plitidepsin	Phase III clinical trials	Depsi-peptide	Tunicate	Various types of cancer	Cell cycle arrest and induction of apoptosis
Gemcitabine	Phase III clinical trials	nucleoside	Sponge	Various types of cancer	Antimetabolite

Table 2. The historical sea creature's metabolites of potent anticancer agents

Compound Name and Number	Structure, Molecular formula, and calculated logarithm of partition coefficient (CLog P)	IC50	Reference
Dibutyl-phthalate; (Compd. 1)	 $C_{16}H_{22}O_4$, Log P: 4.16, CLogP: 4.73	IC50 =10.15 uM	Ref. 50
Di-(2-ethyl-hexyl) phthalate; (Compd. 2)	 $C_{24}H_{38}O_4$, Log P: 7.46, CLogP: 8.706	IC50= 3.79 uM	Ref. 51
Thicoraline; (Compd. 3)	 $C_{48}H_{56}N_{10}O_{12}S_6$, Mol. Wt.: 1157.41	IC50 = 400 pM	Ref. 52
BE-22179; (Compd. 4)	 $C_{47}H_{52}N_{10}O_{12}S_5$, Mol. Wt.: 1109.3	IC50 = 200 pM Not intro-duced in clinical trials. Just in cell lines and preclinical investigations	Ref. 52, 53

Enterocheline Depsipeptide; (Compd. 5)	 $C_{30}H_{29}N_3O_{14}$, Mol. Wt.: 655.56, Log P: -0.35, CLogP: 1.93208	IC50 = 2.5 uM	Ref. 34
Eribulin; (Compd. 6)		IC50 =0.27 nM	Ref. 37
Halichondrin B (Compd. 7)		IC50 = 4.9 uM	Ref. 38, 39
Meleagrin D (Compd. 8)		IC50 of 32.2 uM	Ref. 4, 43

Roquefortine C (Compd. 9)		IC50 of 55.9 µM	Ref. 4, 43, 54
Cembranoid diterpine; (Compd. 10)		(IC50 = > 25 µM	Ref. 55
Epigallocatechin gallate (Compd. 11)		IC 50 = 53 ?M	Ref. 46
Gallic acid (Compd. 12)		IC50 values of 52.7 ± 3.2 µg/ml	Ref. 49

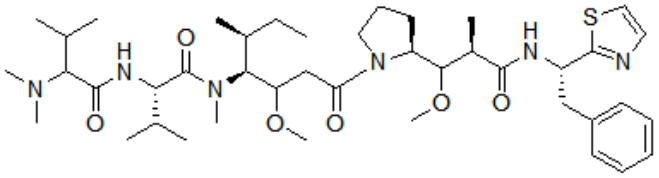
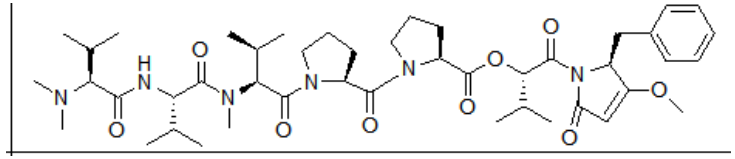
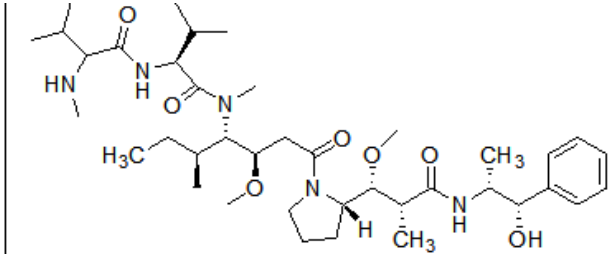
Dolastatin 10 (Compd. 13)		IC50 value 0.5 nM	Ref. 56
Dolastatin 15 (Compd. 14)		IC50 value 3-5 nM	Ref. 38
Monomethyl auristatin E; MMAE (Compd. 15)		Potent and selective vs CD30+ (IC50 less than 10 ng/mL) and in Hodgkin as 1 mg/kg.	Ref. 57

Table 3. Drugs inspired from marine-metabolites in clinical use as anticancer agents

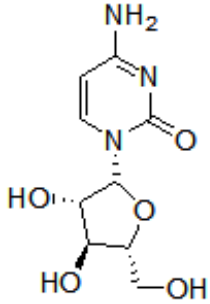
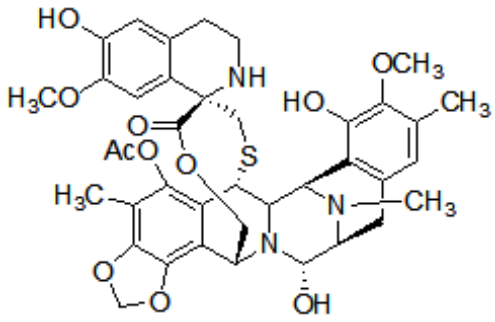
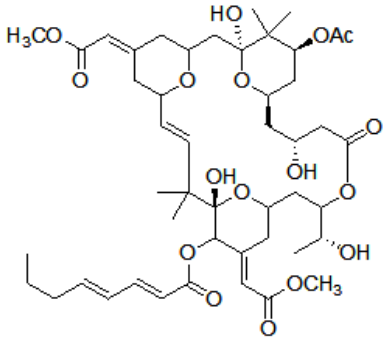
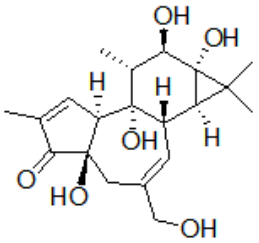
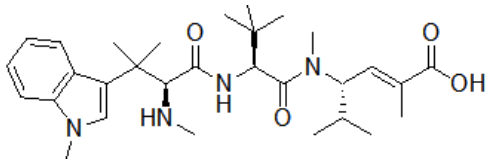
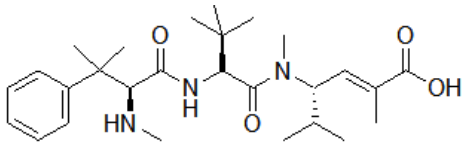
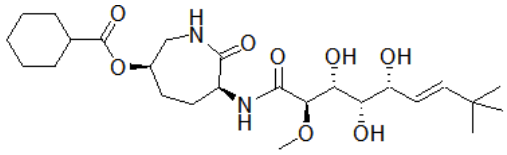
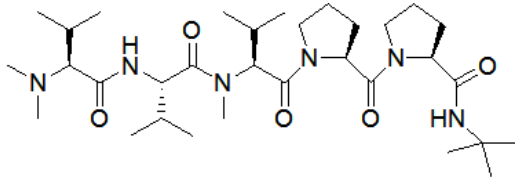
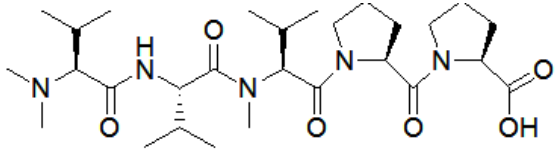
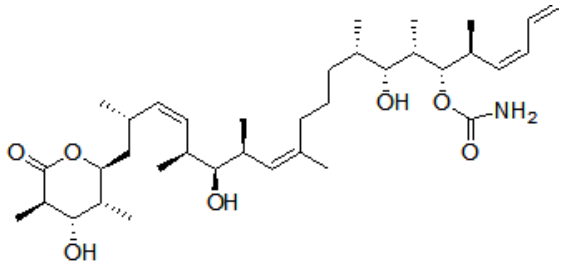
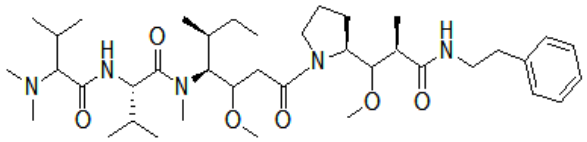
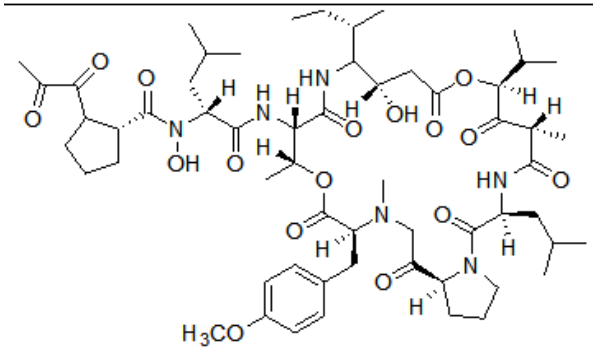
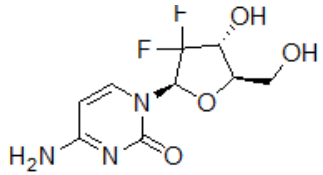
Compound Name and Number	Structure, Molecular formula, and calculated logarithm of partition coefficient (CLog P)	Uses	Reference
Cytarabine (Compd. 16)		Used in treatment of acute non-lymphocytic leukemia, lymphocytic leukemia, and the blast phase of chronic myelocytic leukemia.	Ref. 63, 64
Trabectedin (Compd. 17)		Approved to treat liposarcoma or leiomyosarcoma.	Ref. 42, 65
Eribulin (Compd. 6)	Eribulin acts via a tubulin-based antimitotic approach resulting to inhibition of G2/M cell-cycle, interruption of mitotic spindles, causing apoptosis.	A microtubule inhibitor used to treat metastatic breast cancer and metastatic or unresectable liposarcoma	Ref. 37, 40

Table 4. The candidates of clinical trials as potent anticancer agents.

Compound Name and Number	Structure, Molecular formula, and calculated logarithm of partition coefficient (CLog P)	IC50	Reference
Bryostatin 1 (Compd. 22)		Phase I ovarian cancer, breast cancer, lymphoma, and malignant melanoma	Ref. 96, 97.
Phorbol (Compd 23)		Phase II for advanced colorectal cancer who fail 5-fluorouracil	Ref. 101, 104
Hemiasterlin; E7974 (Compd. 24)		Induces anti-mitotic action result in depolymerisation of microtubules and arrest G2/M phase	Ref. 74

Taltobulin; HTI-286 (Compd. 25)		In colon cancer it showed a tumor suppression effect in breast, ovarian, and lung cancer. It is in clinical phase I trials.	Ref. 105
LAF389 (Compd. 26)		Synthetic bengamide B analogue. In phase I clinical trial was discontinued because it exhibited unexpected cardiotoxicity.	Ref. 108, 109, 111
Tasidotin (Compd. 27)		In phase II against multiple types of cancer 115. (Michigan Cancer Foundation-7), breast cancer, spindle microtubule.	Ref. 114-118
Tasidotin C-carboxylate; ILX651 (Compd. 28)		A tasidotin metabolite. ILX651 phase II for breast cancer, spindle microtubule, microtubules.	Ref. 123
Discodermolide (Compd. 29)		It is useful as a synergistic agent as well as an alternative option to Paclitaxel for tumors that have mutated beta-tubulin and became paclitaxel-resistant as well as other multidrug resistant (MDR) tumors.	Ref. 74, 119, 124

Soblidotin; TZT-1027 (Compound 30)		It is in phase 2 and studies are going on in previously treated non-small cell lung cancer (NSCLC) patients.	Ref. 125
Plitidepsin (Compd. 31)		Plitidepsin plus dextro-methorphan in phase II conducted in relapsed/ refractory patients. It is useful for the management of numerous types of cancers such as: breast and lung cancers (non-small cell), and it is currently in phase III clinical trials	Ref. 126-128
Gemcitabine (Compd. 32)			Ref. 129

mollusks and cyanobacteria. It is composed of an anti-microtubule MMAE linked to a monoclonal antibody specific for tissue factor (TF) through a cleavable linker [74]. TF is highly expressed in many cancer types like prostate, pancreatic, lung, cervical, and breast cancers which are associated with metastasis and since it is a cause of poor prognosis of the disease, TF is considered an attractive target for anticancer agents. TF is also called thromboplastin or factor III and it is mainly expressed in three types of cells which are: perivascular cells, fibroblasts and the cells of the smooth muscles in the sub-endothelial walls of blood vessels and normally it plays a role in the extrinsic pathway of coagulation of blood through activation of factor VII.[72- 91]

In cancer, TF is implicated in angiogenesis (new blood vessels formation), tumor migration and advancement. The way which Tisotumab Vedotin acts by is through binding to TF and incorporation into the cell to release MMAE that then will induce its direct microtubule disrupting effect to kill the cell and its neighbouring cells through a bystander killing effect. Tisotumab Vedotin is currently under phase I clinical trials in a hope to treat different types of cancer like metastatic or relapsed cervical cancer. Cervical cancer is usually treated with first-line therapy consisting of bevacizumab along with paclitaxel and cisplatin or paclitaxel and topotecan but the problem associated with first-line therapy is the low survival and high relapse rates risk so there is a need for out of danger and powerful agent that can enhance the clinical outcomes of treatment.[91]

Tisotumab Vedotin was given as *i.v.* dosage of 2 mg/kg, body weight in a cycle of 3 weeks (to allow normalisation of neutrophils count) and it exhibited a promising antitumor effect in solid tumors especially in case of metastatic or relapsed cervical cancer [91-92]. The most reported side effects were nausea, vomiting, weakness, anaemia, peripheral neuropathy, conjunctivitis, and bleeding from the nose.[91-93]

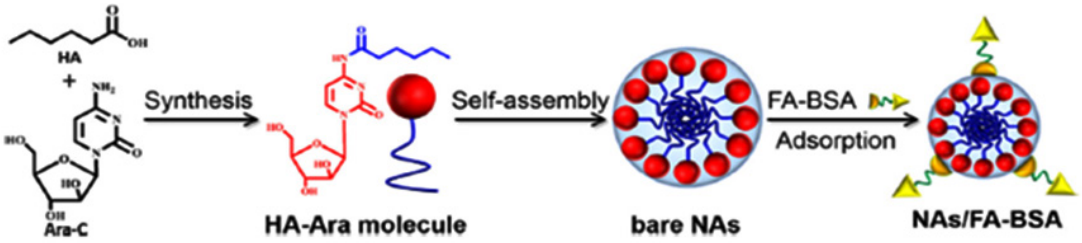
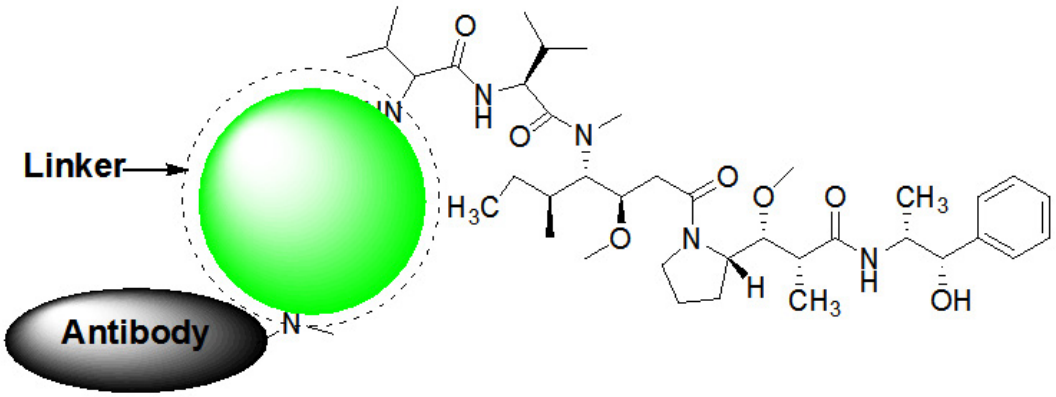


Fig. 1. Nano-assembly of amphiphilic cytarabine prodrug molecules



Brentuximab Vedotin (Compound 18): Antibody = antibody targeting CD30.
Pinatuzumab Vedotin (Compound 19): Antibody = antibody targeting CD22.
Glembatumumab Vedotin (Compound 20): Antibody = antibody targeting GPNMB.
Tisotumab Vedotin (Compound 21): Antibody = antibody targeting TF.

Fig. 2. Antibody-drug conjugates (ADCs)

Anticancer Agents in Clinical Trial Phase 1

Phase I clinical trials can be divided into phase I(A) and phase I(B) trials. Dose escalation administration where a single administration of the doses in phase I(A), and multiple or daily administration in phase I(B) were done.[94-95]

Bryostatin 1 (Compound 22)

It is a macrocyclic lactone that is derived from marine bryozoan *Bugular neritina* and it can also be isolated from other organisms like sponges and tunicates. Bryostatin 1 is in clinical studies (phase I), to determine its activity against different types of cancer and it showed positive results in the management of ovarian cancer, breast cancer, lymphoma [97] and malignant melanoma.[96]

There are 20 different bryostatins that have a general molecular formula of $C_{47}H_{68}O_{17}$ [61, 96, 98]. The mechanism of antineoplastic effect of bryostatin 1 was through binding to protein kinase C enzyme (PKC) and alteration of cellular activity. PKC is a family of serine/threonine specific kinases that have a major role in cell growth and death regulation [99-100]. PKC is activated by calcium or diacyl-glycerol. PKC has a carboxyl terminal catalytic domain and an amino terminal regulatory domain with ATP and phorbol (Compound 23) binding sites respectively. Both of pryostatin 1 and phorbol ester bind to the same binding site in the regulatory domain but the difference is when bryostatin 1 binds, it induces antineoplastic effect while phorbol ester induces effect that promotes tumor formation.[96-101] The cells exposed to bryostatin 1 for short period, PKC was activated resulting in three effects which are proliferation suppression, differentiation induction and promotion of apoptosis in cancer cells. Longer term exposure led to down-regulation of PKC and inhibition of its activity. Bcl-2 is implicated in human diffuse large cell lymphoma and its inhibition by bryostatin 1 has a beneficial effect in treatment.[99-102]

The Phase I trials suggested bryostatin 1 as a single agent will not have encouraging effect while it will have better effect when given in combination with other agents like cytarabine or paclitaxel for treating multiple cancer types. In clinical trial phase I, Bryostatin 1 is currently being tested against other diseases like HIV and Alzheimer's disease, its side effects include lethargy, vomiting, and muscular pain.[103] One of the disadvantage of bryostatin 1, is that it is only produced and obtained in small quantities from its marine source and this problem can be resolved using bacterial gene expression to produce more bryostatin 1 that can be applied in biomedical and biotechnological procedures.[96-99]

In phase II the efficacy and toxicity of bryostatin 1 were assessed for patients with advanced colorectal cancer who have had previous 5-fluorouracil therapy. The primary end point was tumor response. All 25 patients had disease progression within four cycles. Myalgia was the most common toxicity. Myelo-suppression was not seen. The compound as a weekly 24-hour continuous infusion lacks single-agent antitumor activity in advanced colorectal cancer.[104]

Hemiasterlin and Taltobulin

Hemiasterlin; E7974 (Compound 24, Table 4) and Taltobulin; HTI-286 (Compound 25, Table 4) (a synthetic analogue) are tripeptides isolated from different marine sponges like *Hemiasterella minor, Siphonochalina, Cymbastela* or *Auletta* species. E7974 and HTI-286 tested in phase I clinical trials to treat tumors that express high level of p-glycoproteins and become resistant to Paclitaxel and Vincristine. Hemiasterlin works by inducing an antimitotic action that will result in depolymerisation of microtubules and cell cycle arrest at G2/M phase.[74] The *in-vitro* and *in-vivo* assessments of HTI-286 were compared with vincristine and paclitaxel and found more potent in cell growth inhibition, proliferation suppression and apoptosis induction. It was not affected by p-glycoprotein and drug efflux pump overexpression especially in case of colon cancer. It also showed a tumor suppression effect in other types of tumor cell lines like malignancy, lung, ovary, and breast cancer.[105]

Microtubules are important components of the cell cytoskeleton, and they have an important key aspect in maintaining the shape of the cellular components, internal movement, and cellular division through polymerisation and depolymerisation. They have their role in the formation of the mitotic spindle [106-107]. Microtubules are consisting of subunits called alpha-tubulin and beta-tubulin, microtubules form cylindrical tubes.[74, 105-107]

LAF389

LAF389 (Compound 26, Table 4) is a synthetic bengamide B analogue. LAF389 in phase

I clinical trial was discontinued because it exhibited cardiotoxicity. Bengamide B isolated from *Jaspidae sponges* [110]. LAF389 possess both anti-proliferative and anti-angiogenetic properties.[108-110] In addition to preclinical investigations that offer a broad antitumor activity. It is characterized as potent methionine amino-peptidase (MetAP) inhibitor, which inhibits both MetAp1 and 2 directly or indirectly. Inhibition of MetAP will cause cell cycle arrest as MetAP is responsible for DNA repair process, cell transformation, and trade in secretory vesicles and infection.[111-113]

Metabolites of Clinical Trial Phase 2

The studies of clinical trial phase II are performed on a group of few hundred patients and designed to determine the optimum dose of a potential drug that will induce therapeutic effect. The examples of some aquatic natural products that are in phase II clinical trials have been mentioned as below.

Tasidotin

Dolastatins are group of linear peptides originally obtained from hare *Dolabella auricularia* formed by cyanobacteria. Tasidotin and its C-carboxylate (Compounds 27, 28, Table 4) are synthetic third generation dolastatin-15 analogue (Compound 15). One of the major Tasidotin metabolites is C-carboxylate (Compound 28) modifies the dynamic stability of microtubules in a comparable way to Tasidotin but was 10 to 30 times more stronger [117]. The hydrolytic product of Tasidotin has activity on polymerization however, it appears to give less cytotoxic activity.[114-118]

Anticancer Metabolites in Clinical Trial Phase 1/2

Discodermolide

Discodermolide (Compound 29, Table 4) is a polyketide obtained from sponge *Discodermia dissolute.* It undergoes phase I/II trials and has showed a good antitumor activity and in the treatment of several cancers like those affecting breast, ovaries, and lungs. Before being known to have a cytotoxic effect, Discodermolide was considered as an immunosuppressant as was shown during *in-vitro* and *in-vivo* testing. Discodermolide is a microtubule-stabilizing agent that promotes microtubule polymerization and prevents depolymerization resulting in cell cycle arrest at G2-M phase and inhibition of mitosis, therefore it acts in a way like that of paclitaxel or even more potent.[119-120]

So, it is useful as a synergistic agent as well as an alternative option to Paclitaxel for tumors that have mutated beta-tubulin and became paclitaxel-resistant as well as other multidrug resistant (MDR) tumors. The information about structure-activity-relationship (SAR) for semi-synthetic approaches to improve pharmacokinetics (PK) properties of discodermolide-analogues were reported. [74,119]

Soblidotin

Soblidotin; TZT-1027 (Compound 30, Table 4) is a sea-derived peptide of an aquatic origin isolated from marine bacterium *Salinispora tropica*, it is in phase I and II clinical trials. Soblidotin is a newly developed dolastatin 10 analogue that has multiple activities.[4, 120-121] The main difference between soblidotin and the parent drug dolastatin is the terminal dolaphenine amino-acid residue in dolastatin that is replaced in soblidotin by phenylamine group, however, the two compounds have similar activity inhibiter of polymerization of tubulin via attaching to vinca peptide site. In 2002, Soblidotin started its phase I clinical trial, and is currently in three different phases I, II and III in many companies. Soblidotin tested against lung cancer with a mechanism of tubulin inhibition and vascular disruption.[121] Some researchers have found that it inhibits microtubule polymerization, hinder the microtubule assembly/ disassembly balance via interaction with tubulin. It also has anti-vascular action that destroyed the new tumor vasculature. It stops the cell cycle at two phases G2 and throughout to Bcl-2 phosphorylation followed by activation of caspase-3 pathway that led to apoptosis.[120-122]

Anticancer Compounds in Clinical Phase III Trials

Phase III trials representing the full-scale assessment of treatment.

Plitidepsin

Plitidepsin (Compound 31, Table 4), a natural marine cyclic depsipeptide called as (Aplidin®). However, it is accessible now by chemical synthesis.[74] It was fundamentally sequestered from a mediterranean tunicate *Aplidium albicans*. It is useful for treating breast and lung cancers and is in clinical trial phase III

studies.[127] Furthermore, clinical trial (Phase I and II) studies of plitidepsin showed brilliant anti-tumor property in patients with multiple myeloma, advanced medullary thyroid carcinoma, non-Hodgkin's lymphoma, advanced melanoma and urothelium carcinoma.[128]

Plitidepsin aggravate cell cycle arrest dose-dependently and results to apoptosis in cultured cells obtained from solid tumors [127]. These outcomes are linked to the provocation of early oxidative stress by stimulation of Rac1 GTPase and the inhibition of protein phosphatases which in concurrence cause the prolonged activation of c-Jun N-terminal kinase (JNK) and p38 MAPK.[74]

Gemcitabine

Gemcitabine (Compound 32, Table 4) is an anticancer nucleoside (fluorinated derivative of cytarabine) metabolic inhibitor which is a synthetic version of pyrimidine nucleoside analog acting as a prodrug in which the atoms on the 22 carbon of deoxycytidine is substituted by fluorine atoms. Gemcitabine is presently in phase II & III clinical studies.[129] It has been used for the management of numerous carcinomas of pancreas, bladder, breast, and lung cancer (non-small cell). It is used as a primary treatment for pancreatic cancer alone and in conjunction with cisplatin for the management of late-stage or metastatic bladder and lung cancer (non-small cell).[74]

When transported into the cell, gemcitabine is transformed into the functional form which is difluorodeoxycytidine diphosphate (dFdCDP). Then it is subsequently changed into difluorodeoxycytidine triphosphate (dFdCTP) via deoxycytidine kinase and both forms inhibit the progression of DNA synthesis.[74]

Limitations of Aquatic Metabolites and Sources as a Basis of Anticancer Agents

It is confirmed that using the bioactive agents from aquatic sources lead to the invention of new active drugs that made a big difference and would be attractive to most drug inventors worldwide. Nonetheless, taking into consideration some restrictions that may hinder the study of aquatic compounds which is as followings: the low amounts of bioactive agents from the organisms, some inorganic salts in addition to some toxins may be present due to the environment or even the organisms themselves.[1]

Hence, an exertion should be done to identify the potential adulterant to make marine extracts suitable with in vitro testing. Numerous diagnostic procedures are now accessible for the identification, and isolation of active components in marine extracts.[130-131]

Recommendations to Overcome Supply Problems

The controlled aquaculture techniques are the best option to solve the dependency of the variety of chemical compounds (chemo-type) produced by an organism on environmental conditions. These techniques might fend off the issue of exhausting the aquatic resources but also could be a practical option to produce the desired biomass for the scaled-up production needed in a drug discovery pipeline. Furthermore, improvements in chemical synthesis techniques and combinatorial chemistry provided satisfactory solutions for appropriate sourcing.[132]

At last, the cellular markers for most of the newly found marine natural products are undiscovered; therefore, various screening techniques along with proteomics and metabolomics should be mingled to blown away the constraints of in-vitro techniques.

A significant concern for aqua-derived drug discovery is the permanent accessibility of adequate quantity of these organisms and their metabolites without causing injury to environment. If obtaining from natural sources cannot be achieved in a sustainable way, alternative approaches exist to solve the issue of marine supply, like:

Biotechnological Cultivation

Most aquatic organisms cannot be easily cultured in an artificial environment, so co-cultivation process (mixed fermentation of two organisms or more to make the environment like their environment) is used and it will significantly increase chemical diversity and improve the yield of marine-derived compounds production.

Genetic Engineering

It is the transfer of a compound genetic materials and information to the inside of a host cell to produce the desired compound in a sustainable manner, but the exact genetic information must be known to avoid wrong genes insertion.[114]

Synthetic or Semi-Synthetic Adjustments

Both techniques can be used to transform a readily available compound into a final desired product, and these are economic alternatives for

total synthesis to have variable structures and enhance the product characteristics.[133]

CONCLUSION

Secondary metabolites obtained from aquatic sources represent a wonderful area of underexplored but magic weapons that can be used against cancer. The currently available therapeutic approaches have faced limitations on their way for cancer treatment in terms of either side effects or emergence of strains resistant to treatment. Cytarabine, Trabectedin, Eribulin Mesylate and Brentuximab Vedotin are anticancer drugs that have gained the approval from FDA and EMA to be used clinically for cancer treatment. Other compounds are still undergoing different clinical trials phases for their safety and efficacy. Marine is a treasure that must be researched well and exploited.

Improvement of chemical synthesis and aquaculture or isolation processes can be utilized to overcome the issues mentioned. Other approaches like biotechnological cultivation, genetic engineering and synthetic or semi-synthetic modifications are to be used to solve supply problems and obtain aqua-derived compounds in high yield to guarantee a sustainable and effective production.

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Conflict of interest

The authors certify that there is no conflict of interest in this review.

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