Marine anticancer drugs and their relevant targets: a treasure from the ocean

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Abstract

Marine organisms comprising animals and plants are wealthiest sources of bioactive compounds possessing various pharmacological properties specifically: free radical scavenging, antitumor, antimicrobial, analgesic, neuroprotective and immunomodulatory. Marine drugs provide an alternative source to meet the demand of effective, safe and low-cost drugs that are rising with the continuously growing world population. Cancer is one of the leading reasons of mortality in western nations in contrast to communicable diseases of developing nations. In spite of outstanding developments in cancer therapy in past three decades, there is still an insistent necessity for innovative drugs in the area of cancer biology, especially in the unexplored area of marine anticancer compounds. However, recent technological innovations in structure revelation, synthetic creation of new compounds and biological assays have made possible the isolation and clinical assessment of innumerable unique anticancer compounds from marine environment. This review provides an insight into the anticancer research so far conducted in the area of the marine natural products/synthetic derivatives, their possible molecular targets and the current challenges in the drug development.

Keywords Marine bioactive compounds · Antiproliferation · Cell death · Cytotoxic · Apoptosis · Autophagy

Introduction

Marine environment is considered as a foremost reservoir of the millions of bioactive compounds having possibility to be applied in different disciplines like medicine, technology and food. During past 50 years, key compounds substantiating their potential for industrial development as functional foods, nutritional supplements, pharmaceuticals, enzymes and therapeutic agents have been provided by marine sources [1, 2]. A wide range of bioactive compounds of plant origin are presently in clinical/preclinical trials or in the advanced stages of exploration. Though marine compounds are under-explored at present but predictably in the future era, marine milieu would be the treasured reserve for the future unique compounds as it embodies 90% of the biosphere [3, 4].

Interestingly, reports have shown that natural products sequestered from marine invertebrates are often of bacterial or cyanobacterial derivation. Nevertheless, these microbes, usually cannot be cultivated alone as their symbiotic association with higher organisms is imperious for their growth. Many of the genes responsible for the biosynthetic ability remain unexpressed in vitro, if they are cultivated under axenic

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conditions [5]. Invertebrates covers majority of the animals living in the marine milieu in terms of variety and dispersal as well. This makes obvious reason for focusing utmost of the scientific studies related to marine drug invention on these organisms. In retort to the harsh, severe and fluctuating habitats of ocean these organisms generate a broad range of unique secondary metabolites that are not present in terrestrial ones. Compiled data from scientific studies [6] have showed that approximately 80% of the existing Marine Natural Products (MNPs) were belonged to the phyla Porifera and Cnidaria with 47.1% and 33.5% respectively. The remaining of them were belonged to the phyla Echinodermata, Chordata, and Mollusca with 7.4%, 6.0% and 5.0% correspondingly (Fig. 1). Marine environment also represents a huge ecological reserve encompassing a range of aquatic plants and animals that are endowed with vivid antimicrobial, immunomodulatory, anti-inflammatory, anticancer, neuroprotective, analgesic, and antimalarial activities [7].

Cancer comprise the group of diseases in which some of the body's cells begin to divide continuously and have potential to invade or migrate to other body parts. The last two decades have seen outstanding progress in cancer research. However, despite striking innovations in understanding the depth of the cancer & its prevention and treatment, the disease continues to affect millions of people worldwide dreadfully. Numerous factors are associated with the disease that makes its therapy as one of the challenging tasks in medical science. Moreover, another face of the cancer's complexity is compounded with financial, policy and regulatory blockades that has slowed the rate of development against cancer. Despite many breakthroughs, the treatment for most cancers is still a long way from reality.

Marine milieu encompasses a treasure of strong biological composites for e.g. alkaloids, steroids, terpenes, peptides, and polyketides [8]. Remarkably, marine-derived compounds and oncotherapy are interrelated since very beginning as evident
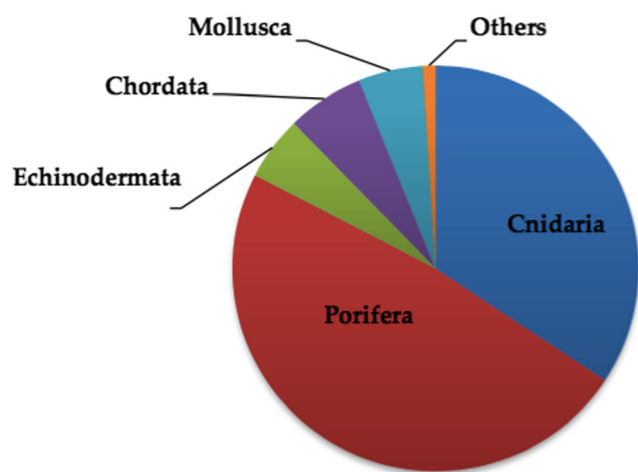

Fig. 1 Representation of the different phyla according to the % of the existing Marine Natural Products (MNP) as per Leal et al. [6]

by one of the first marine-derived clinically used drug, Spongothymidine discovered in 1945 [9–11]. To date, there are variety of marine based compounds in distinctive clinical studies phases and number of constituents already has been scanned for laboratory and animal studies. Nevertheless, evolvement of marine derivatives as therapeutic agents is still in its emergent phase. A primary obstruction is the uninterrupted and continuous supply of the profuse quantity of required creatures and their derived compounds without disturbing the marine milieu at the same time. Moreover, unlike earthly habitations there is lack of written medical scripts of marine-derived compounds. Since last few decades, noteworthy efforts have been made to sequester and categorize novel marine-derived products. If we could be able to resolve these obstacles in a financial and an ecologically safe manner, then only marine drugs development can rise.

This publication is envisioned to showcase the details of several marine natural compounds, approved drugs, derivatives and some other products of medicinal value which are advancing through anticancer clinical trials with the details of their molecular targets and current challenges of the drug development process so far.

Marine milieu: At a glance

The Ocean encompasses one of the wealthiest ecosystems on earth that is a natural habitat for an extensive diversity of living organisms. It is imperative to note that surviving circumstances in the oceans vary drastically from terrestrial ones. Moreover, the biodiversity in the oceans vary in different zones and places. Factors that accounts for this variation includes huge ranges in temperature (from ice sea to deep hydrothermal systems), pressure, light and nutritional conditions. Such taxonomic diversity also makes the basis of chemical diversity, a factor imperative for new drug development. Interestingly out of 36 animal phyla reported, a total of 32 phyla are represented in the marine environment out of which 15 varieties are absolutely present in the marine environment [7].

Marine environment comprises of vast range of fauna (fishes, sponges, tunicates, soft corals, nudibranchs, sea hares, sea slugs, mollusks, echinoderms, bryozoans, prawns and shells) and flora (various types of microorganisms including bacteria, cyano- & actinobacteria, fungi, micro/macroalgae, halophytes [salt-resistant or salt-tolerant plants] and mangroves [tropical coastal vegetation]) [12]. One striking characteristic of marine life is the intimate associations between different groups of organisms so as to adapt themselves to grow in the harsh and challenging ocean conditions that are fundamentally different from those in terrestrial region. One crucial consequence of this adaption results in the production of secondary metabolites that functions in intra- and interspecies signaling, dissuasion of herbivores, competition with neighbors,

inhibition of microbial invasion and protection against radiation and predators. Such properties of these chemicals account for their enormous potential to serve as bioactive compounds or future candidate drugs [5].

Marine pharmacology

Marine pharmacology is a relatively new branch of pharmacological sciences that explores and study the substances having active pharmacological properties present in marine species of plants and animals. Marine natural products are usually secondary metabolites having no primary function associated with the development, growth or propagation of a species. A comparative study has already confirmed the superiority of marine based natural products over earthly natural products in relation to chemical distinctiveness [13].

Marine anticancer agents (faunal derivatives)

Cancer is a global deadliest disease whose projected worldwide frequency is about 6 million cases per year. Many innovations have already been made or continued in the development of all already existing measures; nevertheless, some of the problems are unresolved yet for e.g. Heterogeneity of the cancer cell subpopulation, development of resistant phenotypes and its recurrence. These obstacles demand the elaboration of new tactics and molecules for drug discovery. Our interest in marine ecosystems has been accelerated in last two decades although in the chronicle of pharmacology, references to marine-based remedies are rare. Nonetheless, a number of marine compounds with diversified chemical structures has been screened [14] and reported for variety of activities for e.g. antimicrobial, antiparasitic, antitumor and anti-inflammatory [15].

Interestingly, National Cancer Institute had reported in preclinical cytotoxicity testing that the ratio of the terrestrial versus marine samples in exhibiting anti-tumor profile is approximately 1:10 [16]. At present, 08 drugs sequestered from sea milieu have already been accepted for distinctive tenacities (cytarabine, ziconotide, vidarabine, acid ethyl esters, eribulin mesylate, trabectedin, iota-carrageenan and brentuximab vedotin) [17]. Out of these, five have been permitted as pharmaceutical medicines in cancer therapy namely, cytarabine (first marine-derived clinically used drug), trabectedin, eribulin mesylate, ziconotide and brentuximab vedotin [17]. The list of some marine faunal anticancer compounds and derivatives is shown in Table 1.

Approved marine anticancer drugs

Current Anticancer drugs of marine origin approved for human use worldwide are as follows:

Cytarabine The breakthrough came in the discovery of marine-based cytostatic agents with the unearthing of the nucleosides spongothymidine and spongouridine derived by caribbean sponge *Tethya crypta*, that were discovered serendipitously. Grounded on this invention, the synthetic referend cytosine arabinoside cytarabine (Fig. 2) has been established as an effective antileukemic agent [18, 19] that was subsequently permitted by Food and drug administration, (FDA) U.S. in 1969. Side effects include gastrointestinal toxicity, diarrhoea, intestinal ulceration, oral mucositis and septicemia. Temperature rise and increase of hepatic enzymes are fairly common, that however do not signify therapeutic troubles [20].

Mechanism of action Pyrimidine nucleoside is a chemical nature of cytarabine that acts as a prodrug. Inside the cells it is transformed to cytosine arabinoside triphosphate, which damage DNA by competing with the biological substrate deoxycytidine leading to the inhibition of DNA polymerase and eventually synthesis of DNA [4, 5, 18, 19].

Trabectedin It is isolated from the ascidian *Ecteinascidia turbinate* an inhabitant of Mediterranean and Caribbean Sea. The animals live on corals and generate the compound as a safeguard against microorganisms. Trabectedin molecule is an alkaloid of tetrahydroisoquinoline class (Fig. 2). In 2007, Trabectedin was the first anticancer molecule of marine source that got approval in European Union (EU) to treat reverted incidents of platinum-sensitive ovarian cancer and sarcoma (soft-tissue) [21]. It was approved by FDA in 2015. This drug has been reported to show hepatoxicity and hematologic side effects in various studies. It was reported that patients with alcohol abuse, underlying liver disease/elevated bilirubin or hematologic abnormalities may not be the best candidates for this drug [22].

Mechanism of action It is noteworthy to state that Trabectedin is an anti-neoplastic compound that acts on unwanted proliferative cells and also on the tumor micromilieu as well. Cytostatic action of Trabectedin is contributed by its binding ability to the DNA minor groove and consequently preventing transcription by inhibition of the DNA binding of transcription factors. Moreover, it cooperates straight by the RNA polymerase II. It is known to affect the micromilieu of tumor by controlling the quantity of tumor-linked macrophages and thus in turn regulating the production of angiogenic factors and cytokines [4, 5, 21].

Eribulin mesylate It is a synthetic analogue of marine natural product halichondrin B, extracted from sponges for e.g. *Halichondria okadai* and *Lyssodendoryx* sp. It comes under polyketides nontaxane derivatives (Fig. 2). The medication was permitted by the FDA in 2010 and subsequently by the
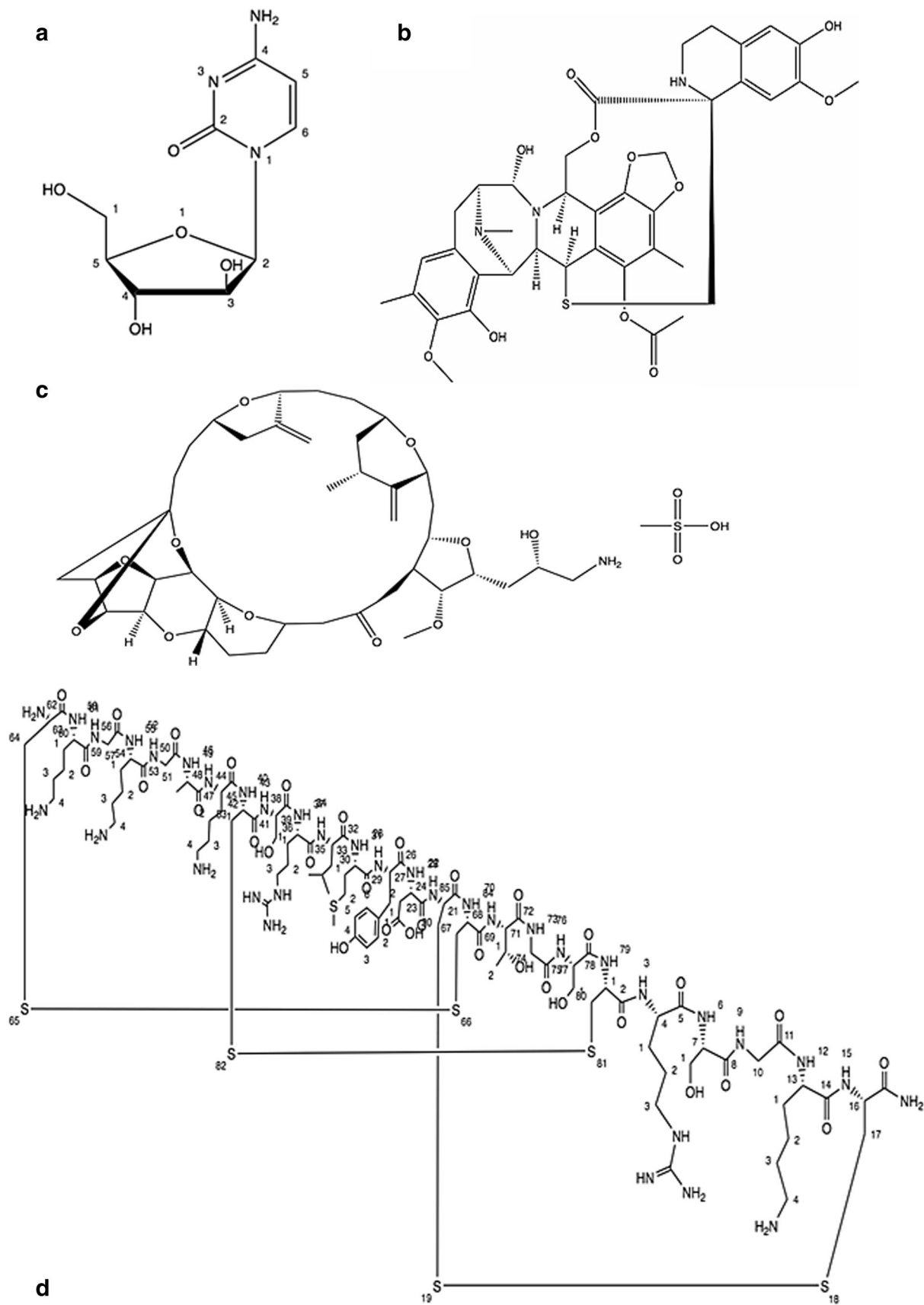
Fig. 2 Approved marine anticancer drugs. (**a**) Cytarabine, (**b**) Trabectedin, (**c**) Eribulin mesylate and (**Dd**) Ziconotide

EU in 2011 as an anticancer drug for patients with locally advanced or metastatic breast cancer. Some related side effects of this drug include neutropenia, peripheral neuropathy, mild alopecia, cough and fatigue [23].

Mechanism of action It acts by influencing the microtubule dynamics. It inhibits the progression phase of microtubules and further segregates the tubulin into nonproductive masses thus results arrest in G2/M phase of the cell cycle and apoptosis [24].

Brentuximab vedotin Brentuximab vedotin combines an effective cytotoxic agent together with a tumor targeted specific monoclonal antibody (Fig. 3). FDA U.S. in 2011 gave approval to the Brentuximab vedotin for the management of patients of systemic ALCL (anaplastic large cell lymphoma) and reverted as well as refractory Hodgkin lymphoma. It comprises cytotoxic compound (antimitotic agent) monomethyl auristatin E (MMAE) and an antibody targeted against CD30 (cell-membrane protein) belong to the surface of tumor cells but found rarely on normal cells (Fig. 3). The antibody and cytotoxic components are linked through an enzyme-cleavable peptide-based linker bonds (valine-citrulline dipeptide) [25, 26]. Auristatin, synthetic referend of the marine-based natural invention Dolastatin 10, is a linear depsipeptide. Dolastatins embodies a series of cytotoxic peptides formerly isolated from the Indian Ocean mollusk *Dolabella auricularia* but in very small quantities. At present dolastatins are obtained by cyanobacteria of the genus *Symploca* [27]. Side effects reported with this drug are fatigue, low platelet count, diarrhea and hepatotoxicity.

Mechanism of action Its high toxicity makes it unfeasible for its use alone but by aiding with conjugated antibody it can be focused specifically for tumor cells. Brentuximab vedotin interacts with the extracellular domain of CD30 receptor present on tumor cells that subsequently gets internalized by the clathrin-assisted endocytosis. Ultimately as it comes to

lysosome, lysosomal proteases cleave the linker peptide and MMAE gets released into the cytosol [28] where it binds tubulin and prevents polymerization leading to G2/M cell cycle arrest and finally to Apoptosis (programmed cell death). Interestingly, it has been studied that interaction of MMAE into the micromilieu of the CD30 expressing cells can impact CD30 lacking lymphoma cells too [29].

Ziconotide It was the first drug of marine origin to obtain approval in 2004 from the FDA (U.S.) to ameliorate severe and chronic pain. It was originally extracted from the venom of sea snail named as magical cone (*Conus magus*). It is the mock derivative of a ω-conotoxin peptide (Fig. 2).

Mechanism of action Ziconotide exploits a selective N-type voltage-gated Ca^{2+} (calcium) channel as an inhibitor. Eventually it impedes the release of neurochemicals like glutamate, substance P in the brain and spinal cord and calcitonin gene-related peptide that accounts for pain relief [30]. Ziconotide is administrated intrathecally for management of varied neuropathic/nociceptive pain in cancer and non-cancer patients too [31]. Although it was reported that use of Ziconotide induces some adverse effects like nausea, rise in creatine kinase levels and rhabdomyolysis but it doesn't work out to make the possibility of refusing the drug as it must be decided on an individual basis [32]. Mild side effects reported are nausea, dizziness, vomiting etc.

Marine anticancer compounds in clinical phase III trial

Plitidepsin It is a natural marine cyclic depsipeptide (features a peptide chemical structure) but now accessible via chemical synthesis (Fig. 4). It was primarily sequestered from a Mediterranean tunicate *Aplidium albicans* found in the Mediterranean Sea. For the management of numerous neoplasias comprising breast and lung cancers (non-small-cell), it is currently in phase III stage of clinical studies [17]. It has been reported to elicit apoptosis at low nanomolar (nM) range of
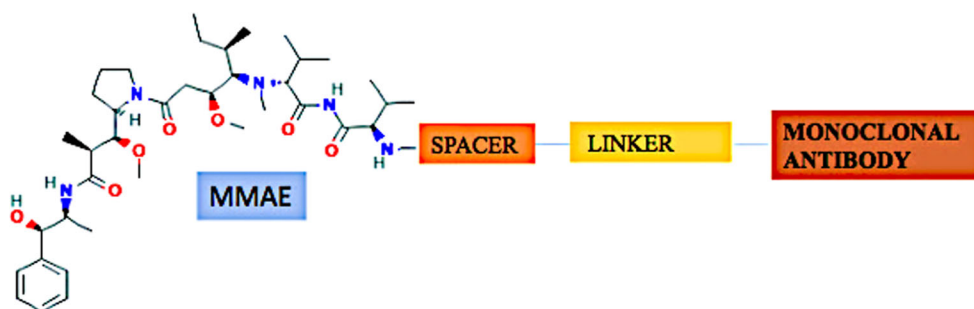

Fig. 3 Schematic representation of the structure of Monomethyl Auristatin E -Monoclonal Antibody (MMAE-MAB)-conjugate. Basic structure of the MMAE-conjugate is same except the difference of monoclonal antibody which is targeted against specific factor as described below: Tisotumab vedotin = MMAE + Spacer- Linker +Tissue Factor (TF) targeting antibody. Pinatuzumab vedotin = MMAE + Spacer-Linker+ CD22 targeting antibody. Glembatumumab vedotin = MMAE + Spacer- Linker +glycoprotein NMB (gpNMB) targeting antibody. Brentuximab vedotin = MMAE + Spacer- Linker +CD30 targeting antibody
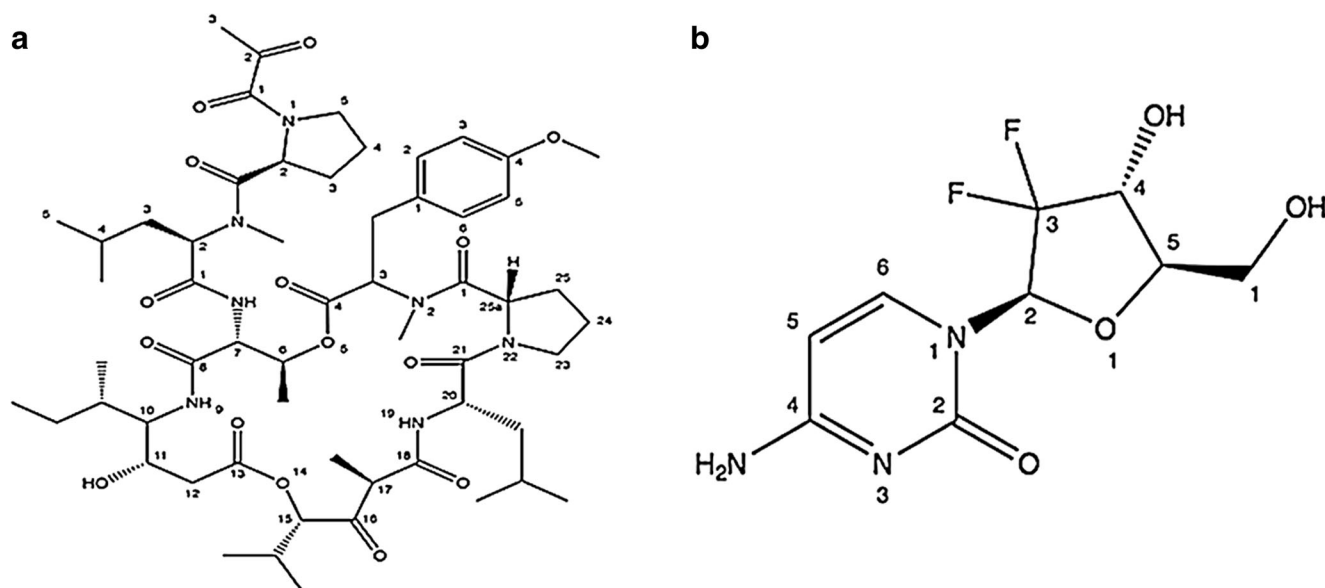
Fig. 4 Marine anticancer compounds in clinical phase III trial. (**a**) Plitidepsin and (**b**) Gemcitabine

IC50 values. Moreover, clinical trial (Phase I and II) studies of plitidepsin showed brilliant antitumor property in patients with multiple myeloma, advanced medullary thyroid carcinoma, non-Hodgkin's lymphoma, advanced melanoma and urothelium carcinoma [33].

Mechanism of action It provokes cell cycle arrest dose-dependently and leads to apoptosis in cultured cells obtained from solid tumors [16]. These consequences are linked to the provocation of early oxidative stress via 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 [34].

Gemcitabine (dFdC) It is an anticancer nucleoside (a fluorinated derivative of cytarabine) metabolic inhibitor. It is a synthetic version of pyrimidine nucleoside analog acting as a prodrug in which the hydrogen atoms on the 2′ carbon of deoxycytidine are substituted by fluorine atoms (Fig. 4). It is currently in phase II & III clinical studies [35, 36] being used for the management of numerous carcinomas of pancreas, bladder, breast and lung cancer (non-small cell) [37]. Gemcitabine is used as a prime treatment for pancreatic cancer alone and also in conjunction with cisplatin for the management of late-stage or metastatic bladder and lung cancer (non-small cell).

Mechanism of action Once transported into the cell, gemcitabine is transformed into the functional form difluorodeoxycytidine diphosphate (dFdCDP) and subsequently into difluorodeoxycytidine triphosphate (dFdCTP) by deoxycytidine kinase. Both forms restrain the progression of DNA synthesis. dFdCTP contends with deoxycytidine triphosphate (dCTP) and is incorporated into DNA, a most possible mechanism of gemcitabine induced cell death. Consequent to the assimilation of gemcitabine nucleotide on the end of the elongating DNA strand during replication, one more deoxynucleotide is added and afterwards the DNA polymerases becomes incapable to proceed further. This phenomenon apparently screws the drug into DNA because of the fact that proofreading enzymes becomes incapable to remove gemcitabine from its location. Additionally, dFdCDP impedes ribonucleotide reductase, thereby reducing the deoxynucleotide pool accessible for DNA synthesis. The decline in the intracellular concentration of dCTP potentiates the incorporation of dFdCTP into DNA [38]. To sum up, Gemcitabine metabolites serve to augment the overall inhibitory actions on cell growth.

Marine anticancer compounds in clinical phase II trial

Soblidotin It is isolated from sea hare *Dolabella auricularia* of the Indian Ocean. It is a synthetic derivative of the dolastatin backbone from dolastatin 10 (Fig. 5). Presently it is undergoing phase II clinical tests.

Mechanism of action Soblidotin is a vascular disrupting agent that specifically causes collapse to tumor vasculatures along with its tubulin inhibitory activity and cytotoxic effect [39]. It inhibits microtubule polymerization and interferes with microtubule assembly/disassembly equilibria through interaction with tubulin.

Elisidepsin (PM02734) It is a marine based mock cyclic depsipeptide that belongs to the compounds of Kahalalide family (Fig. 5) [40]. It is isolated by a sacoglossan (sap-
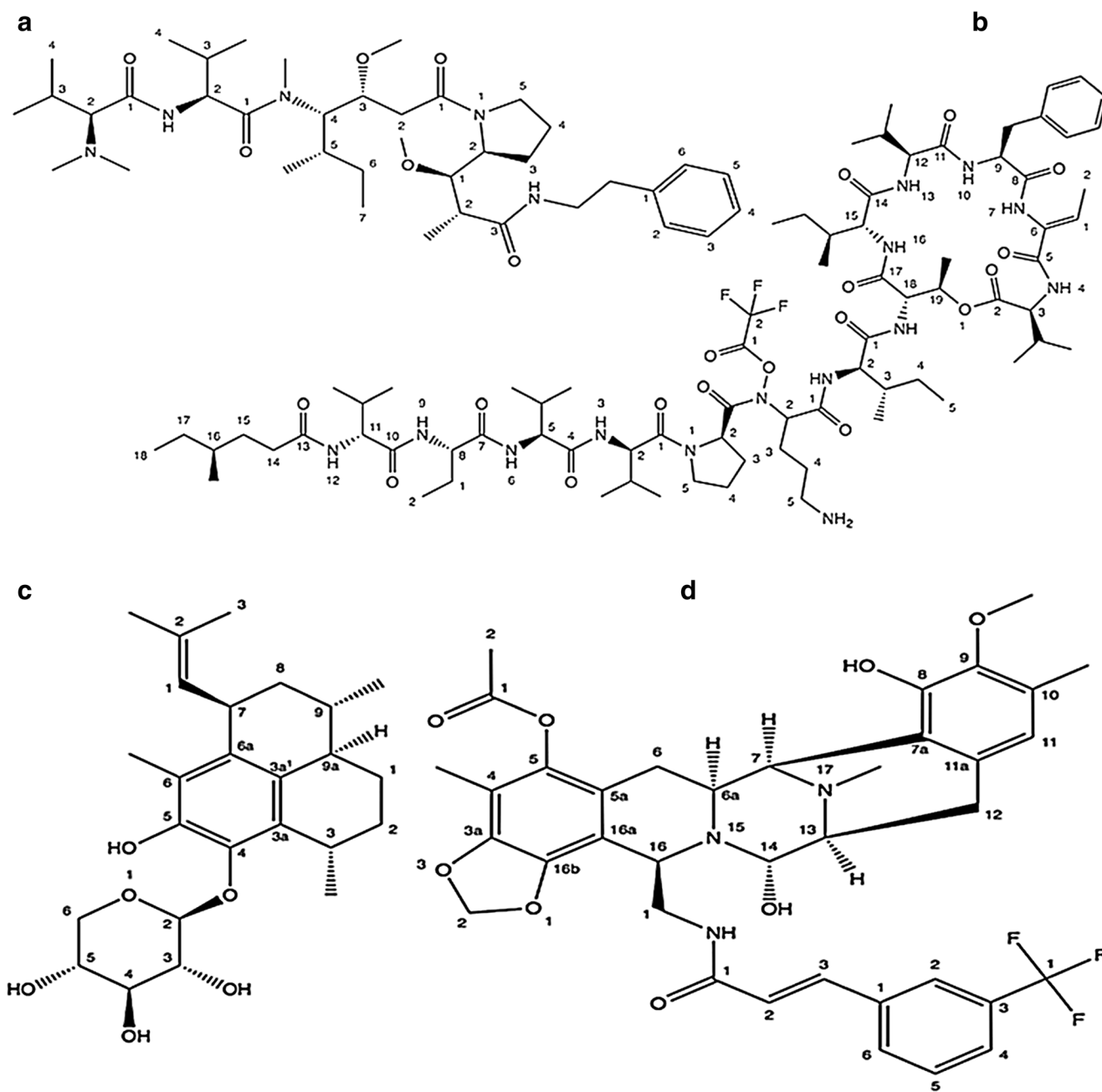
Fig. 5 Marine anticancer compounds in phase II clinical trial. (a) Soblidotin (b) Elisidepsin (c) Pseudopterosins and (Dd) PM1004

sucking sea slugs) slug, *Elysia rufescens* (herbivorous marine Indopacific mollusk) and belongs to the Kahalalide family (dehydro aminobutyric acid-containing peptides) of compounds. It is undergoing Phase II clinical studies for its antitumor property and promising therapeutic index [21]. It has been reported to have effective in vitro cytotoxicity against diverse human tumor cell lines, which may be because of oncolytic cell death induction instead of apoptosis [21].

Mechanism of action Although its mechanism of action is still debated, it has been reported that it provokes caspase-free/independent demise of cell linked with characteristics of autophagy

(or autophagocytosis) via reticence of the Akt/mTOR based signaling and stimulation of death-associated protein kinase (DAPK, a family of serine/ threonine kinases) [41].

Glembatumumab vedotin It is one of the fully-human monoclonal antibody-drug conjugate (ADC) obtained from mollusks and cyanobacteria. At present, it is in phase II clinical trial, used for the management of breast cancer and melanoma [42].

Mechanism of action It is targeted against a glycoprotein NMB (gpNMB) (Fig. 3), that is reported to be overexpressed

in various cancers. gpNMB has been shown to be linked with the metastasis. CR011, a gpNMB-targeting antibody is allied to an effective cytotoxic monomethyl auristatin E (MMAE) thus forming an antibody-drug conjugate (ADC). Interestingly, Glembatumumab vedotin is stable in the bloodstream and linker is broken to liberate monomethyl auristatin E once internalize into gpNMB-expressing tumor cells eventually causing cytotoxicity. It is currently in progress for the management of local advanced or metastatic breast cancer [43].

Pseudopterosins It belongs to diterpene based glycosides (Fig. 5) acquired by the coral (soft coral) *Pseudopterogorgia elisabethae*. It had been reported to exhibit effective wound-healing and anti-inflammatory property in phase II clinical studies [44].

Mechanism of action Pseudopterosin A is a strong phorbol myristate acetate inhibitor. It has been reported to cause topical inflammation in a mouse model with degranulation of human polymorphonuclear leukocytes and prevents phagosome creation in tetrahymena cells. In a double-blind Phase II clinical trial pseudopterosins were found to enhance re-epithelialization process in the early wound repair process [21]. Recently it has been shown that Pseudopterosin impedes the NF-κB signaling thus blocks the pro-inflammatory cytokine liberation in breast cancer cells and the corresponding interaction with accompanying immune cells [45].

PM1004 It has been reported as a synthetic analogue of tetrahydroisoquinolone alkaloid (Fig. 5). Structurally it is similar to a natural alkaloid, jorumycin sequestered from the Pacific nudibranch *Jorunna funebris* [46, 47] and additionally it is also reported to be found in sponges and tunicates [47]. It has been reported as an effective chemotherapeutic compound in the management of solid type human tumors and blood malignancies. At present it is in phase II clinical studies [47, 48].

Mechanism of action It is a novel alkaloid with DNA-binding capability leading to the cell cycle arrest and impairment of transcription.

Marine anticancer compounds in clinical phase I/II trial

Discodermolide It is a polyketide (Fig. 6) isolated from the deep-water marine sponge *Discodermia dissoluta* by Gunasekera and co-workers and currently undergoing phase I/II clinical trials [48]. Discodermolide has been reported as an effective inhibitor of tumor cell growth in several MDR (Multidrug resistant) cancer cell lines and shows immunosuppressive properties both in vitro and in vivo [49, 50].

Mechanism of action It acts as a microtubule-targeted drug. It stabilizes microtubules by preventing the depolymerization of microtubules [51]. Consequently, it arrests mitosis because of microtubule bundling and impediment of the separation of sister chromatid pairs thus induces G2-M cell cycle arrest [52].

Marine anticancer compounds in clinical phase I trial

Bryostatin 1 It belongs to macrocyclic lactones (Fig. 7) sequestered from the marine based bryozoan *Bugula neritina* (Bugulidae). Interestingly, it has been reported to possess both antineoplastic and immunopotentiating properties. Bryostatin has been reported to possess various properties for e.g. T cell activation, immunomodulatory action and activation of haematopoietic progenitor cells.

Mechanism of action Bryostatin 1 possess high binding affinity to cysteine rich domains of protein kinase C (PKC) results in its triggering and further translocation to the cell membrane. Subsequent to the phosphorylation of specific protein substrates, PKC gets ubiquitinated and finally directed for proteolysis. Bryostatin 1 acts synergistically with other anti-cancer agents by down-regulating PKC thus enhancing their cytotoxicity. Bryostatin 1 has been reported to the stimulate tumor cell differentiation and inducing apoptosis in tumor cell [53, 54]. Moreover, it also shows immunomodulation, cytokine release stimulation and expansion of tumour specific lymphocyte populations [55, 56]. These may be the possible base for both immunostimulating and anticancer properties.

Pinatuzumab vedotin It is an antibody-drug conjugate, isolated from mollusks and cyanobacteria. It comprises of the potent antimicrotubule agent monomethyl auristatin E (MMAE) conjugated to an antibody (CD22) (Fig. 3). CD22 is a B lymphocyte-specific adhesion molecule of the Ig superfamily found on the surface of most B cells. It regulates signaling related to antigen receptor and regulates B cell function, survival and apoptosis. Pinatuzumab vedotin is targeted to manage malignancies of B cell including many leukemias and lymphomas.

Mechanism of action Upon binding to CD22 expressing cells, pinatuzumab vedotin is internalized consequently releasing the cytotoxic agent that eventually leads to microtubule disruptions and cell death. Pinatuzumab vedotin has been reported to show inhibitory action against Non-Hodgkin Lymphoma (NHL) and Chronic Lymphocytic Leukemia (CLL) [57]. It is imperative to note that CD22 receptor expression is limited to B-cells and also exist on NHL and CLL.

Tisotumab Vedotin It is one of the antibody-drug based conjugate (Fig. 3) isolated from mollusks and cyanobacteria. It is
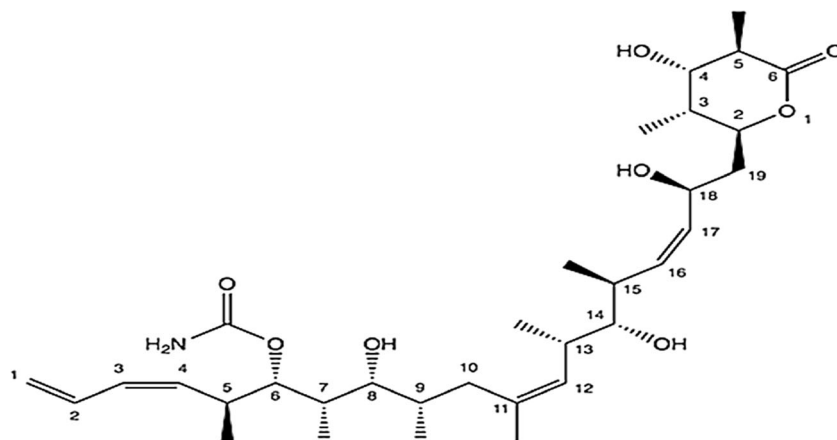
directed against Tissue Factor (TF), a protein reportedly involved in tumor signaling and angiogenesis [58, 59]. Tissue Factor (TF) is considered as a potent target for antibody-drug conjugates since it is found to be vastly expressed on many solid types of tumors.

Mechanism of action Tisotumab vedotin includes an antibody targeting Tissue Factor (TF) conjugated with monomethyl auristatin E (MMAE) via a cleavable linker. TF is aberrantly expressed in a broad type of solid tumors including cervical cancer and is associated with poor prognosis [58, 59]. Upon binding to TF expressing tumor cells, Tisotumab vedotin is internalized after which the cytotoxic agent is released resulting in microtubule disruptions and further cell death. Release of MMAE in tumor microenvironment also induces bystander killing of neighboring cancer cells.

HTI286 (Taltobulin) It is a synthetic derivative (Fig. 7) belong to a small family of naturally occurring cytotoxic peptides, Hemiasterlins. These were formerly originated from extracts of marine sponges (*Cymbastela* sp., *Hemiasterella minor, Siphonochalina* sp., and *Auletta* sp.). Hemiasterlins are tripeptides containing three sterically congested amino acids [60–62]. Hemiasterlin (E7974) is a compound that is currently in phase I clinical studies. It is highly efficient in inhibiting the growth of paclitaxel and vincristine resistant tumors associated with P-glycoprotein overexpression.

Mechanism of action Hemiasterlin is an effective cell growth inhibitor that leads to microtubules depolymerisation and cell cycle arrest in the G2-M phase [63].

LAF389 It is a synthetic derivative (Fig. 7) of a class of marine natural products, bengamides. Bengamides are biological products originally sequestered from Jaspidae sponges [64]. Bengamide B is one of the most effective members of the family. LAF389 has antiproliferative, antitumor & antiangiogenetic properties [65].

Mechanism of action Bengamides acts by inhibiting the action of methionine amino peptidases (MetAps) directly or indirectly [66]. MetAP is involved in the functioning of numerous factors involved in DNA repair mechanism, signal transduction, cell transformation, secretory vesicle trafficking and infection. Its inhibition leads to cell cycle arrest.

PM060184 It comes under the group of tubulin binding agents that was initially sequestered from the *Lithoplocamia lithistoides*, a marine sponge but at present obtained by synthetic production (Fig. 7). Interestingly, it is under clinical trials in patients with advanced stages of cancers. PM060184 has been documented to have the highest known affinities among tubulin binding agents and targets tubulin dimers at new binding site by reducing microtubule dynamicity [67].

Mechanism of action It covalently fixes to the residues resides in the minor groove of DNA. Consequently, it results in suspended progression through S phase of the cell-cycle, arrest in the G2/M phase and subsequent apoptosis.

NVP-LAQ824 It is an indolic cinnamyl hydroxamate (Fig. 7 and Table 1) currently in clinical (phase I) studies on the patients having tumors and leukemia. It is a synthetic compound derived from marine natural product Psammaplin A, a symmetrical bromotyrosine disulfide possessing oxime groups. NVP-LAQ824 has been reported to show potent in vitro antitumor activity. It is interesting to mention that Psammaplins have been sequestered from a variety of sponges and the brominated aromatic amino acid byproducts are shared by marine bacteria. This suggests that these metabolites may truly derive from biosynthetic pathways of microorganisms living in association with such sponges.

Mechanism of action NVP-LAQ824 inhibits histone deacetylase enzymatic activities. NVP-LAQ824-induced apoptotic signaling involves up-regulation in the expression of p21, activation of caspases and cleavage of poly adenosine diphosphate (ADP) ribose (PARP) [83].
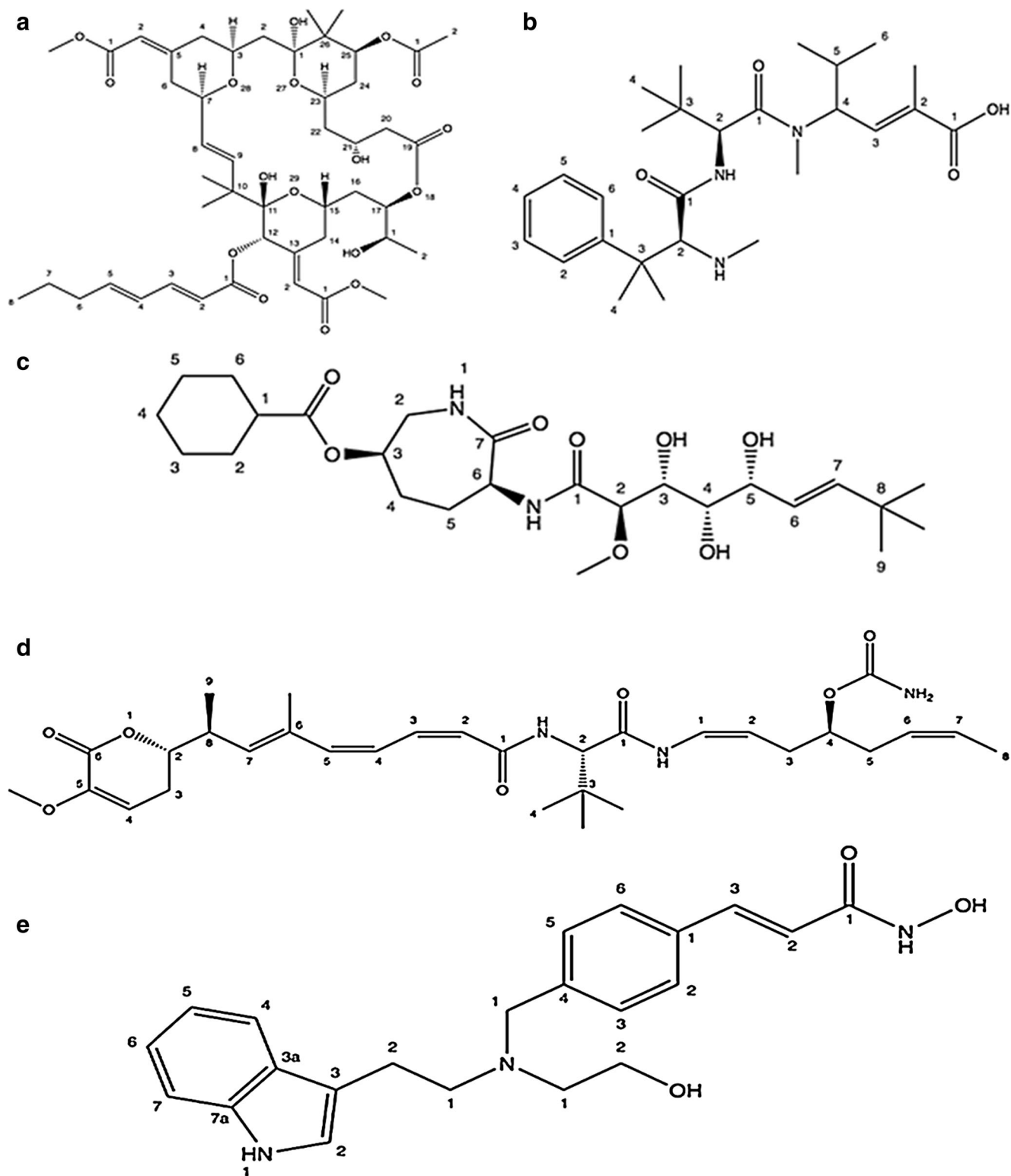
Fig. 7 Marine anticancer compounds in phase I clinical trial. (**a**) Bryostatin, (**b**) Taltobulin, (**c**) LAF389, (**d**) PM060184 and (**e**) NVP-LAQ824

Table 1 Some representatives of the marine faunal derived anticancer compounds and derivatives

Marine Organism	Compound	Activity	Mechanism of action	References
Reniera sarai, renamed *Haliclona* (Rhizoneira) *sarai* (Marine sponge)	3-alkylpyridinium polymers	Cytotoxic against non-small cell lung cancer	Upregulation of pro-apoptotic and down-regulation of anti-apoptotic proteins, mitochondrial depolarization.	[68]
Sinularia flexibilis (Soft coral)	Sinulariolide	Antiproliferative on A375 melanoma cells	Induce apoptosis by mitochondria-mediated & caspase-dependent pathways.	[69]
Pseudoceratina sp. (Marine sponge)	Dibromotyrosine Derivative	Cytotoxic activity against K562 cells.	IKK/NFκB signaling pathway, caspases-3 and − 9 activation, PARP cleavage.	[70]
Dicathais orbita (Marine gastropod)	tyrindoleninone and 6-bromoisatin	Anticancer on leukemia, lymphoma and colorectal (HCT-116) cell lines.	Cell-cycle arrest and apoptosis inducer.	[71]
Fascaplysinopsis bergquist sp. (Marine sponge)	Fascaplysin	Anticancer against small cell lung cancer cell lines.	DNA-intercalating capability, cyclin-dependent kinase 4 (CDK4) inhibitory activity.	[72]
Xestospongia sp. (Marine sponge)	Araguspongine	Cytotoxic	Autophagic cell death, inhibitor to receptor tyrosine kinases, suppression of PI3K/Akt/mTOR signaling.	[73]
Holothurioidea, Echinodermata (Sea cucumber)	Triterpene glycosides	Antitumor, cytotoxic	Cell-cycle arrest, regulation of extracellular signal-regulated kinase (ERK), Focal adhesion kinase (FAK).	[74]
Sphyrna tiburo (Bonnethead sharks)	Epigonal conditioned medium (ECM)	Cytotoxic	Caspase activation, PARP cleavage, activation of apoptotic proteins.	[75]
Marthasterias glacialis (Star fish)	Ergosta-7,22-dien-3-ol and Palmitic Acid	Cytotoxic	Cell-cycle arrest, apoptosis by C/EBP homologous protein (CHOP)–mediated pathway of ER-stress.	[76]
Smenospongia aurea	Smenamides A and B	Pro-apoptotic, cytotoxic	Cytotoxic activity at nanomolar quantities on lung cancer (Calu-1) cells.	[77]
Ianthella sp. (Australian marine sponge)	Lamellarin O	Cytotoxic against colon cancer cells	Inhibit ABC transporters that induce MDR.	[78]
Callyspongia siphonella	Sipholane triterpenoids (sipholenol A, sipholenone E, sipholenol L, and siphonellinol D)	Cytotoxicity enhancer of other cancer drugs, reverse chemoresistance.	Specific inhibitors of Pgp (P-Glycoprotein), increase the intracellular accumulation of drugs.	[79]
Haliclona (Soestella) *mucosa*	Panicein A	Cytotoxic against human melanoma cell lines	Enhance the cytotoxic and proapoptotic action of doxorubicin	[80]
Kirckpatrickia variolosa (Antarctic sponge)	Variolin B	Anti-tumor and antiviral compound	DNA intercalator	[81]
Mycale hentscheli	Peloruside A	Cytotoxic	Effect microtubule dynamics, abnormal spindle formation.	[15]
Agelas dendromorpha and Cymbastella sp.	Agelastatin A	Antineoplastic	p53-independent Apoptosis inducer, Wnt signalling inhibitor	[82]

Marine anticancer compounds (floral derivatives)

Marine milieu floras comprise micro flora, micro/macro algae and various flowering plants. Since prehistoric time's marine based floras have been used traditionally for medicinal tenacities especially in Asia (India & China) and Europe. The list of marine floral anticancer compounds and derivatives is shown in Table 2.

MNPS cancer molecular targets: An updated knowledge

In the year 2000 two researchers Hanahan and Weinberg proposed [121] in their report, the characteristic and harmonizing proficiencies which allow cancer development and metastatic propagation in the form of six major hallmark: "self-sufficiency in growth signaling, insensitivity to antigrowth signals, evading apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis". A decade later in the way of outstanding progress in cancer study consequent to this publication, an updated review [122] and revisited concepts added 2 emergent hallmarks: "reprogramming of energy metabolism and evading immune response and two enabling traits: instability of genome and mutation and inflammation that promotes tumor". Fouad and Aanei [123] in 2017, attempted to present a more systematized and revised depiction of the cancer in the form of seven hallmarks: "selective growth and proliferative advantage, altered stress response favoring overall survival, vascularization, invasion and metastasis, metabolic rewiring, an abetting microenvironment, and immune modulation". In this section, we will focus upon the cellular targets, modulated by the MNPs and their contribution to their anticancer profile.

Anti-tubulin agents

Microtubules are filamentous cytoskeletal proteins that play a crucial role in intracellular migration and transport of vesicles, cell shape maintenance, polarity, signaling and mitosis thus serves as an imperative therapeutic target in tumor cells [124]. Microtubules constitutes the mitotic spindle in dividing cells and are extremely dynamic and sensitive to number of therapeutic inhibitors thus supports the fact, why such compounds that alters microtubule action have established to be extremely functional in cancer patients. In the field of cancer before the conception of targeted therapy, microtubules were the solitary alternative to DNA as a therapeutic target. Microtubules encompasses head-to-tail arrangement of heteropolymers having α-, β and γ-tubulin forming dimers

that further arranges itself into 13 protofilaments (arranged in parallel manner) forming a rigid hollow structure.

A variety of chemically distinct compounds deriving from natural (terrestrial or marine) or synthetic sources interacts with tubulin and/or microtubules, thus alters its polymerization and dynamics in diverse ways. Such compounds are said to be antimitotic representatives that impede cell proliferation by binding and destroying microtubule dynamics, either growing (polymerization) or shortening (depolymerisation) at susceptible mitotic stage.

Antimitotic drugs that targets microtubule is usually classified into two chief groups: the microtubule-destabilizing and stabilizing agents. As suggested by the name itself, "Destabilizing" antimitotic agents obstruct polymerization of the microtubule at the high drug concentrations. Most of compounds that belongs to this group interacts in one of the two domains present on tubulin, namely the "Vinca" domain & the other i.e. "Colchicine" domain. Compounds that binds on Vinca site include the cryptophycins, vinca alkaloids, eribulin, rhizoxin, dolastatins, spongistatin, tasidotin and maytansinoids. Colchicine-site binders include colchicine and its analogs. Another class i.e. "microtubule-stabilizing" antimitotic agents augment the polymerization of microtubule at high concentrations of the drug. Some of the marine compounds as Anti-tubulin agents are listed in Table 3 and their mechanism of action is depicted in Fig. 8.

Inducers of apoptosis and autophagy

Defective apoptosis signifies as a chief contributing element in the growth and progression of cancer. The capability of tumor cells to escape engagement of apoptosis play a noteworthy role. Cancer cells do this by deregulating the signals that leads to apoptosis in normal manner and thus become masters of their own destinies. By understanding the intricacies of apoptosis and the machineries developed by tumor cells to resist commitment of cell death, strategies can be developed to selectively induce apoptosis in cancer cells.

Apoptotic implicates the genetically programmed abolition of cells involved in development, differentiation, normal cell turnover and most important, in the removal of damaged/ stressed or harmful cells that is otherwise likely to induce the tissue hurt and local inflammation [125]. A variety of pathological ailments including cancer can results from the dysregulation of the apoptotic program alteration by imbalance of pro- & anti-apoptotic signals [126]. It occurs by two core pathways i.e. extrinsic death receptor pathway [127] or intrinsic pathway [128] which are initiated either by extracellular death receptors such as FAS, TNF-α, and TRAIL or by intracellular stimuli such as irreparable genetic damage, hypoxia, severe oxidative stress, and nutrient deprivation. Both the pathways allied to the expression of ligands as a signal for

Table 2 Some representatives of the marine anticancer floral derivatives/compounds

| Marine flora	Chemical constituent	Biological Activity	Mechanism of action	References
Bacteria				
Salinispora tropica and *Salinispora arenicola*	Salinosporamide A (Marizomib)	Anticancer on multiple myeloma, lymphoma, glioblastoma, can cross blood-brain barrier.	Proteasome inhibitor.	[84]
Streptomyces variabilis	Ammosamides	Anticancer agaist neuroblastoma, colon carcinoma.	Cell cycle modulators, inhibitors of quinone reductase 2, Tubulin polymerisation inhibitors.	[85]
Halomonas sulfitobacter (Brine-seawater interface of the Red Sea)	Crude extract	Anticancer	—	[86]
Halophilic sp., chromohalobacter salexigens, Halomonas meridian, Idiomarina loihiensis, Chromohalobacter israelensis (Brine pools of the Red sea and from sediment).	Crude extract	Anticancer	—	[87]
Serinicoccus sp.	Seriniquinone	Anticancer against melanoma.	Autophagy inducer, targets small protein dermicidin.	[88]
Streptomyces sp.	Chlorizidines A and B	Cytotoxic against colon cancer cells.	Target enolase & Glyceraldehyde-3-phosphate dehydrogenase.	[89]
Micromonospora marina	Thiocoraline	Cytotoxic profile for melanoma and cancer cell lines (lung and colon).	Inhibiting DNA polymerase α, induces cell-cycle arrest.	[90]
Fungus				
Aspergillus sp.	Synthetic analogue of metabolite Halimide	Non-small cell lung cancer, Neutropenia, Glioblastoma, Brain cancer.	Guanine nucleotide exchange factor stimulants; Mitosis inhibitors; Tubulin polymerisation inhibitors; Vascular disrupting agents.	[91]
Halorosellinia sp., Guignardia sp.	Anthracenedione	Anticancer	Type II topoisomerase inhibitor; it disrupts DNA synthesis and DNA repair.	[92]
Myrothecium roridum	Verrucarin A	Antitumor	Inhibition of the activation of the mitogen activated kinases c-JUN and p38.	[93]
Penicillium sp.	Chromanone A44	Antitumor	Alteration of carcinogen metabolizing enzymes and protection from DNA damage.	[94]
Microsporum sp.	Neoechinulin A	Cytotoxic effect on human cervical carcinoma HeLa cells	Upregulates p53, p21, Bax, Caspase 3, and Caspase 9 proteins and downregulates Bcl-2.	[95]
Aspergillus fumigatus	Fumigaclavine C	Antiproliferative in MCF-7 cells.	DNA fragmentation, cell-cycle arrest, modulate the apoptotic protein expressions.	[96]
Neosartorya pseudofischeri	Gliotoxin	Antiproliferative in colon cancer cells.	Apoptosis inducer, Wnt signalling inhibitor	[97]
Algae				
Stigonema sp	Scytonemin	Antiproliferative and anti-inflammatory actions, Cytotoxic against human fibroblasts and endothelial cells.	Protein kinase inhibitor.	[98]
Symploca sp.	Largazole	Antiproliferative activity in colon cancer.	Histone deacetylase inhibitor.	[99]
Nostoc sp.	Cryptophycins	Cytotoxicity against human solid tumors.	Microtubule inhibition.	[100]
Caulerpa taxifolia	Caulerpenyne	Cytotoxic, antiproliferating and anticancerous profile.	Inhibition of microtubule polymerization.	[101]
Lyngbya boulloni, Lyngbya majuscula	Apratoxin E, Apratoxin A	Cytotoxic profile against adenocarcinoma.	Inhibits Janus kinase (JAK)/STAT signaling, cell cycle arrest.	[102]

Table 2 (continued)

Marine flora	Chemical constituent	Biological Activity	Mechanism of action	References
Ascophyllum nodosum, Sargassum thunbergii	Fucoidan	Anticancer and fibrinolytic.	Cell cycle arrest, decrease in anti-apoptotic proteins expression, activation of JNK and p38.	[103, 104]
Undaria pinnatifida	Fucoidan	Cytotoxic against human hepatocellular carcinoma SMMC-7721.	Cell death by ROS mediated-mitochondrial signaling pathway.	[105, 106]
Acanthophora spicifera	Ketosteroids	Antitumor, cytotoxic against human cancer cell lines.	Regress viable cell count & volume of tumor.	[107]
Lyngbya majuscula	Curacin A	Antiproliferative in cancer cell lines.	Colchicine Site Antimitotic Agent.	[108]
Sargassum fusiforme, Sargassum trichophyllum	Laminarin	Apoptosis of LoVo human metastatic colon cell	Caspase-3, caspase-9 induction and cell- cycle arrest.	[109]
Laminaria japonica	Fucoxanthin	Antitumor, anti-lung cancer.	Cell cycle arrest, modulates p21, p53, PUMA, Fas, Bcl-2 and caspase-3/8 expression.	[110]
Rhodomela confervoides	Bis (2,3-dibromo-4,5-dihydroxy--phenyl) -methane (BDDPM)	Cytotoxic	Inhibit integrin-FAK signaling.	[111]
Caribbean tunicate Tridiemnium solidum (symbiotic cyanobacterium living in association with the tunicate)	Didemnin B	Antitumor	Inhibits the synthesis of DNA, RNA and proteins	[112]
Monanchora pulchra	Sesterterpenoid and cholestane-type steroids	Antineoplastic	Inhibit Wnt/-Catenin Signaling	[113]
Hippospongia metachromia	Ilimaquinone and ethylsmenoquinone	Antineoplastic	Inhibit Wnt/-Catenin Signaling, p53 activation, apoptosis inducer	[114]
Mangroves and other coastal plants				
Ceriops decandra	Mangrove tea, triterpenes	Inhibit DMBA Induced Hamster Buccal Pouch Carcinoma	Antimicrobial against cancer causing bacteria, Free radical scavenging.	[115]
Acanthus ilicifolius	acanthicifoline and benzoxazinium compounds	Antineoplastic	Apoptosis induer, Free radical scavenging.	[116]
Conocarpus erectus	trimethoxyellagic acid glucuronide	Antineoplastic in MCF-7 snd Hep G2 cells	Cytotoxic, Free radical scavenging.	[117]
Avicienna alba	Naphthoquinones.	Anticancer	Free radical scavenging.	[118]
Calophylum inophylum	Phenylcoumarins, xanthone, biflavonoids, Neoflavonoids.	Anticancer	Cell cycle arrest, decreased Bcl-2 expression, increase expression of Bax, cytochrome C and p53.	[119]
Excoecaria agallocha	Diterpenes, tannin, alkaloids, Exoecarin, Mycertin.	Anticancer	Free radical scavenging.	[120]

Table 3 Some marine anti-cancerous compounds and their molecular targets

S. No.	Molecular targets		Name of the Drugs	References
	Microtubules		Dolastatin-10 (linear pentapeptide), diazonamide A (peptide), scleritodermin A (peptide), Vitilevuamide (bicyclic 13 amino acid peptide), Spongistatins (macrocyclic lactones), Taltobulin (HTI-286, tripeptide), Peloruside A (macrolide polyketide), Zampanolide (macrolide), Dictyostatin (macrolide polyketide), Discodermolide (polyketide), Laulimalide (macrolide).	[15, 124]
	Apoptosis & Autophagy		Nortopsentins A, B & C (imidazolediylbis [indole] alkaloids), Ilimaquinone (sesquiterpene quinone), Frondoside A (glycosylated triterpene), Stelletin A (triterpenoid), Echinoside A (sulfonylated holostane tetrasaccharide) and ds-echinoside A (a non-sulfated triterpene glycoside), makaluvamines (pyrroloiminoquinone alkaloids), Tyrindoleninone & 6-bromoisatin (indole derivatives), Monanchocidin A (guanidine alkaloid), didemnin B, CS5931(Polypeptide), Dolastatin 10, 15 and bryostatin 1 (Polyketides), Jasplakinolide (depsipeptide).	[15, 121–131]
1.1.1.1.	Kinase inhibitors	a. PKC (Protein Kinase-C)	11-hydroxystaurosporine, bryostatin-1, xestocyclamine A, (Z)-Axinohydantoin and debromo-Z-axinohydantoin, hymenialdisine and debromohymenialdisine, frondosins, BRS1, nakijiquinones, spongianolides, lasonolide A, penazetidine A, corallidictyals A and B.	[132–141]
		b. Cyclin Dependent Kinases	(a) Cyclin Dependent Kinase-1 inhibiting marine compounds: Hymenialdisine, Microxine, Variolin B. (b) Cyclin Dependent Kinase-4 inhibiting marine compounds: fascaplysin, Konbu'acidin A, halistanol sulfate.	[133]
		c. Tyrosine Protein Kinase (TPK)	Penta-, hexa- and hepta-prenylhydroquinone 4-sulfates, halenaquinone, halenaquinol, halenaquinol sulfate and xestoquinone, Melemeleone, 14-methoxyhalenaquinone and xestoquinolide.	[133]
		d. Epidermal Growth Factor Receptor	Tauroacidins A and B, Ma'edamine A, Spongiacidins A and B, (+)-aeroplysinin-1, 3,9-dimethyldibenzo [b,d]furan-1,7-diol, 3-(hydroxymethyl)-9-methyldibenzo[b,d]furan-1,7-diol, 1,7-dihydroxy-9-methyldibenzo [b,d] furan-3-carboxylic acid, 3′-norspongiolactone, gracilins, tetrahydroaplysulphurin-1.	[133]
		e. Mitogen-Activated Protein Kinase	Hymenialdisine and debromohymenialdisine, Liphagal 1, Dolastatin, Kahalalide F, Elisidepsin trifluoroacetate, Aplidine (dehydrodidemmin B, DDB, Aplidin), onnamide A and theopederin B.	[133]
	Angiogenesis, Invasion or Metastasis Inhibitors		Geodiamolide H, Stylissamide X, Suberreamoline A, Cortistatin A, Aeroplysinin-1, Motuporamines A, B and C, Bastadin 6, 9 & 16, Phidianidine A, Sceptrin, Latrunculins A and B, Laulimalide, ds-echinoside A, holothurin A and 24-dehydroechinoside A, frondoside A, perhydrobenzoxepine (A & B) and bicyclodecane (C & D), frondoside A, sipholenone A and sipholenol A & E and sipholenone A, Globostellatic acid X, Heteronemin, pachycladins A and D, Sarcophines, inulodurins A and B, Strongylophorine-26, Smenospongine, WA-25, Psammaplin A, Microsporins A and B, Azumamides A–E, Largazole.	[15, 142–149]
	Hypoxia Inducible Factor (HIF) Inhibitors		Laurenditerpenol, Furospongolide, Benzo[g]chromen-4-one and Benzo[h]chromen-4-one, Manassantin B, 7-hydroxyneolamellarin A.	[150–152]
	Topoisomerase Inhibitor		Makaluvamine A, Ascididemin, Lamellarin D.	[153, 154]
	Wnt Inhibitor		Gliotoxin, Fucoidan, cholestane-type steroids, ilimaquinone and ethylsmenoquinone	[97, 106, 113, 114]

Fig. 8 Pictorial representation of the interlinking of various molecular targets of marine anticancer compounds
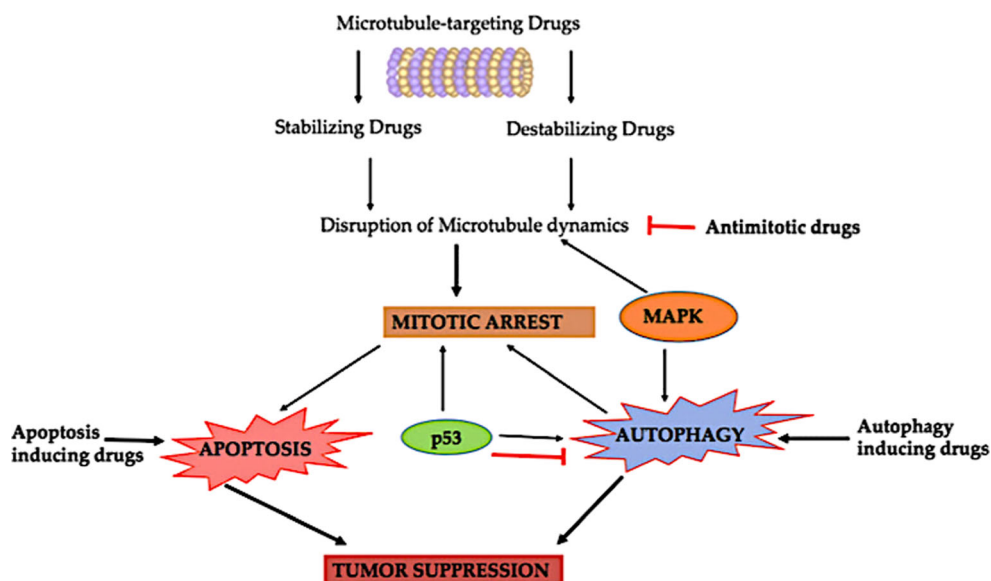
phagocytic cell receptors, caspase-3 cleavage, fragmentation of DNA (DNA laddering), mortification of the nuclear and cytoskeletal proteins, creation of vesicles called apoptotic bodies and ultimately uptake by phagocytic cells [129]. The proteins that belong to Bcl-2 family [130] regulates the intrinsic pathway that results in the release of cytochrome c (Cyt c) from the mitochondria to the cytosol. Cytoplasmic Cyt c together with Apaf-1 and pro-caspase 9 triggers initiator caspase 9 via the creation of a complex known as apoptosome that initiates a protease cascade which consequently activates caspases 3 and 7.

Autophagy, an indispensable and regulated conserved catabolic process principally facilitates the salvaging and turnover of numerous cytoplasmic eukaryotic cell constituents. It is strictly regulated by autophagy-related genes (ATGs) [131]. Autophagy performs a twin part in the regulation of pro-survival under certain circumstances and pro-death signaling pathways in a range of diseases including cancer [155]. Autophagy is frequently stimulated by conditions of hypoxia, accumulation of Reactive Oxygen Species (ROS), nutrient deficit situations, triggering by drugs or under the influence of endoplasmic reticulum stress (ERS). The mTORC1 (mammalian target of Rapamycin Complex 1), PI3K (Phosphatidylinositol 3 kinase), AKT or Protein kinase B, Beclin-1 (mammalian homologue of Atg6) and p53 are chief proteins that play imperative role in autophagy [156]. The regulatory mechanisms of autophagy are still controversial. To figure out the function of autophagy in cancer cell fate, out of numerous theories one proposes that its role fluctuates depending on the stage of tumor development. On one hand, autophagy confines tumor formation in early stages but on other hand it favors tumor cell survival, invasion, and metastasis after tumors formation [157, 158]. Some of the marine compounds as inducer of Apoptosis and autophagy are listed

in Table 3 and their interlinking with other molecular targets are depicted in Fig. 8.

Kinase inhibitors

The enzyme, Protein kinase plays a diverse and dynamic character in cell regulation by regulating signaling pathways involved in numerous processes like cell differentiation, propagation, biotransformation, DNA damage repair, cell-motility and apoptosis [132]. Their deregulation has been reported to cause a number of diseases including cancer, central nervous system disorders, autoimmune and metabolic diseases. Thus, understanding the machinery and directive of several kinases may definitely have potential as a novel medicinal goal. The protein kinase family comprises all enzymes catalyzing the chemical relocation of phosphate (PO_4^{3-}) group (termed as phosphorylation) via a comparatively high energy compound for example ATP (Adenine Triphosphate) to a precise acceptor (substrate). Kinase inhibitors derived from marine sponges were reported in a review [133]. Different types of kinases can be summarized as:

PKC (protein kinase-C)

PKC encompass eleven isozymes and involved in monitoring the task of other proteins through the phosphorylation of hydroxyl groups of amino acids (serine and threonine) residues. Protein kinase-C enzymes are stimulated by signals such as upsurges in the concentration of DAG (diacylglycerol), phosphatidyl serine (PS), inositol triphosphate (IP3) and calcium ions (Ca^{2+}). They are potential therapeutic targets for cancer as they play a fundamental role in signal transduction pathways.

Cyclin dependent kinases

Cyclin Dependent kinases (CDKs) comes under the family of serine/threonine kinases, comprising nearly 25 different cyclin families which perform an imperative role in cell-cycle regulation [134]. Over the past three decades it has been well-defined that the hyperactivity of Cyclin Dependent Kinases (CDKs) is one of the mechanisms involved in the cancer proliferation. As evident by name, their enzymatic activation requires the binding of the regulatory subunit known as cyclin [135]. The variable concentrations of distinctively stimulated CDK/cyclin complexes determine the cell cycle phases whose mechanism of action implicates the phosphorylation of several discrete proteins specifically at threonine or serine residues.

Tyrosine protein kinase (TPK)

Tyrosine protein kinase or Tyrosine kinase includes the enzymes that can catalyze the addition of phosphate group (phosphorylation) especially at tyrosine residues and functions as an "on" or "off" switch in many cellular roles. They are of two types namely; Receptor tyrosine kinase (having an intracellular tyrosine kinase domain, a transmembrane domain and an extracellular ligand-binding domain) & Non-receptor (cytoplasmic) tyrosine kinases. Tyrosine protein kinase are reported to be linked with proliferative ailments for example cancer, leukemia (cancer of the bone marrow), psoriasis owed to their function in controlling key cell tasks like cell growth, delineation and signaling to prevent apoptosis [136].

Epidermal growth factor receptor

The epidermal growth factor receptor (EGFR) is a transmembrane receptor for members of the epidermal growth factor family (EGF family) of extracellular protein ligands. EGFR subfamily comprises erbB-1, −2, −3 and − 4 [137]. It has been reported that cancer could be the outcome of the mutations that disturbs EGFR expression or activity. Overexpression of EGFR is reported to be associated very frequently in cancers, particularly breast cancer [138].

Mitogen-activated protein kinase

A MAPK or MAP kinase (Mitogen-activated protein kinases) comprises a family of proteins that particularly add phosphate group (phosphorylation) at tyrosine, threonine and serine amino acids and intently linked to several cellular assignments of cancer for example cellular division, propagation, cycle, apoptosis, metastasis and angiogenesis [139]. They are stimulated by exterior influences and encourages the transmission of internal (intracellular) signals via the phosphorylation and triggering of related directs that conclusively reach the nucleus and produce a cellular reaction [140]. The three main subclasses that belong to this family includes Extracellular Signal-Regulated Kinases (ERKs), p38 MAPKs and c-Jun N-terminal Kinase (JNK)/Stress-Activated Protein Kinase (SAPKs) [141]. Mitogen-activated protein kinases are often overexpressed or upregulated in cancer cells. It is obvious and reported too that discerning compounds that inhibit these kinases affect cellular proceedings in an extreme specific way and thus they are significantly important in anticancer pharmaceuticals. Some of the marine compounds as kinase inhibitors are listed in Table 1 and interlinking of various subtypes are shown in Fig. 9.

Angiogenesis, invasion or metastasis inhibitors

Angiogenesis besides playing an imperative role in normal physiological activities, also plays a grave part in the development and spread of cancer. As a part of normal physiological process, it occurs during menstruation, placenta formation, pregnancy or organogenesis particularly in a damaged organ and in wound-healing action. Angiogenesis is regulated by an equilibrium of angiogenic inhibitors and stimulators. Moreover, in cancer angiogenesis nourishes tumor progression and spreads diseased cells through the blood to further organs thus provoking the development of secondary malignant growths (metastasis) [142]. Being symbol of cancer [122], angiogenesis is measured as a one of the commanding objective to overpower tumor progression and secondary malignant growths. Numerous factors imperative for targeting the phenomenon of angiogenesis are as follows, i.e., vascular endothelial growth factor-related kinases [143], Matrixins or MMPs (Matrix Metalloproteinases) [144], Methionine Aminopeptidase (a metalloenzyme) [145], Actin, Microtubule [146] and Histone Deacetylases (HDACs) [147]. Hence compounds that impede angiogenesis-linked factors has become an effective target for therapy of cancer. Among them Histone deacetylases (HDAC) are currently being investigated for their use in anticancer therapy. They are group of enzymes involving in the removal of acetyl groups thus playing pivotal role in the regulation of chromatin structure and gene expression. It has been reported that marine sponges and their associations yielded the Psammaplin family of compounds (bromotyrosine derivatives) as a potent histone deacetylase and DNA methyltransferase inhibitors [159]. Moreover, Microsporins A and B derived from marine- fungus *Microsporum* cf. *gypseum* has been documented as potent inhibitors of histone deacetylase and exhibit cytotoxicity against human colon adenocarcinoma (HCT-116) and the panel of 60 cancer cells of National Cancer Institute [160]. Azumamides A–E (cyclic tetrapeptides) isolated from the marine sponge *Mycale izuensis* are another group of histone deacetylase inhibitors [161] but the marine cyanobacterial
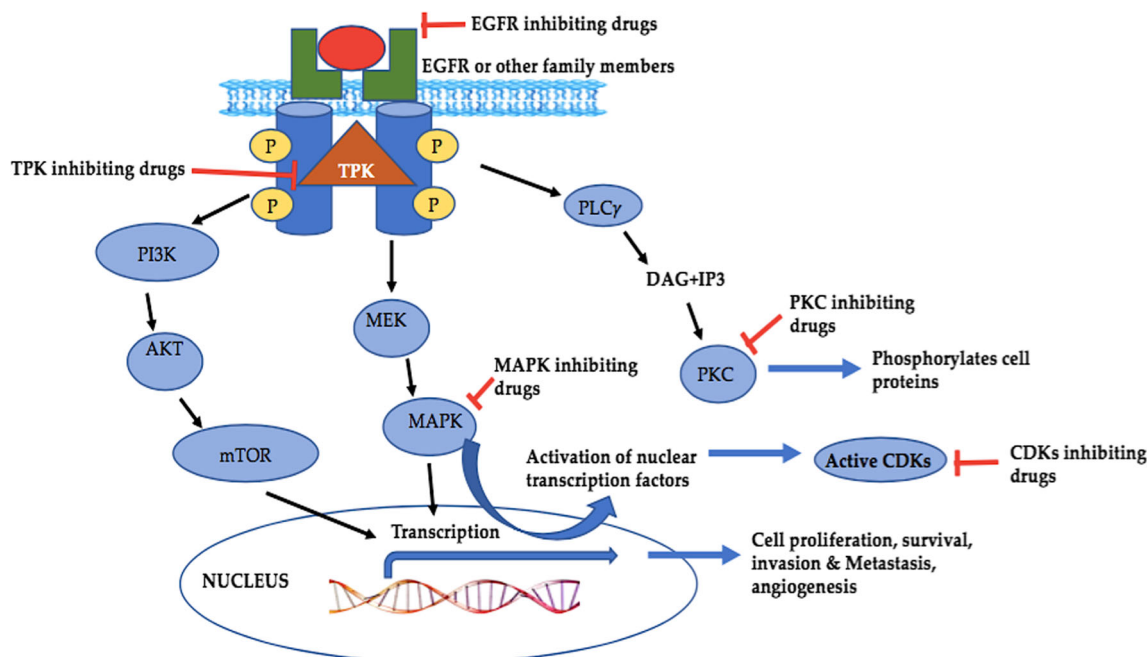
Fig. 9 The relation between different kinases and their cross-talk capable to provoke cell responses involved in the cancer. Abbreviations: EGFR; Epidermal growth factor receptor, PLCγ: Phospholipase C, DAG; Diacylglycerol, IP3; Inositol 1,4,5-triphosphate, CDKs; cyclin- dependent kinases, MAPKs; Mitogen Activated Protein Kinases, MEK; Mitogen-activated protein kinase kinase, TPK; Tyrosine Protein Kinases, mTOR; mammalian target of Rapamycin, PKC; Protein kinase C

metabolite largazole is among the most potent HDAC inhibitors found to date [162]. Interestingly, largazole thiol has been reported to be more active than any other marine-derived HDAC inhibitor such as psammaplin [159] and azumamides [161]. The studies have shown that the involvement of HDACs plays a crucial role in angiogenesis by alterating numerous pro- and anti-angiogenic genes [163].

Metastasis, the extreme feature of cancer determines the clinical stages and prognosis [148]. MMPs, belongs to the zinc-reliant/dependent group of endopeptidases, performing imperative functions in mortification of the Extracellular Matrix (ECM) & also in penetration & the process of metastasis. ICAM-1, Integrins (heterodimeric transmembrane receptors), MMPs and ECM are some of the foremost elements involved in metastasis. Investigations on the formation of new blood vessels (angiogenesis) and metastatic progressions is primarily concentrated on composites that can disturb or regulate these processes thus serving as prospective medications for cancer therapy [149]. Some representative angiogenesis inhibitors are listed in Table 3.

## Hypoxia inducible factor (HIF) inhibitors

Hypoxia-inducible factors (HIFs) are the transcription factors that act to decline available oxygen in the cellular milieu or hypoxia. Transcriptional retort to hypoxia is facilitated by hypoxia inducible factors (HIF1–3). The oxygen-sensitive signal being produced by a sequence of protein hydroxylases catalyze prolyl and asparaginyl hydroxylation on specific residues in the regulatory HIF-α subunits (HIF1α, HIF-2α, and HIF-3α). Tumor progression is associated with intratumoral hypoxia [150] that promotes the growth/formation of blood vessels important for developing a vascular system in embryos and tumors. Additionally, loss of HIF-1 action has been reported to be related to the massive deleterious effects on tumor growth and vascularization [151, 152]. Therefore, numerous compounds that inhibit HIF needs to be targeted with the purpose of discovering a novel way to tumor treatment. Some of the marine compounds as HIF inhibitors [153] are listed in Table 3 and depicted by Fig. 10.

Topoisomerase inhibitors

Topoisomerases are enzymes that participate in the over winding or under winding of DNA thus show a foremost function in supporting the integrity of the DNA helix throughout the vital processes of transcription, replication and mitosis [154]. There are compounds known as Topoisomerase inhibitors that hinders the act of topoisomerase (topoisomerase I and II). Latter is an enzyme that regulates the alterations in DNA organization by accelerating the breaking and retorting of the phosphodiester back of the DNA. They impede DNA replication process and transcription thus results in the demise of cells trying to undertake these progressions. Therefore, they are now being directed for anticancer treatment. Some of the

Fig. 10 HIF as a molecular target for cancer treatment
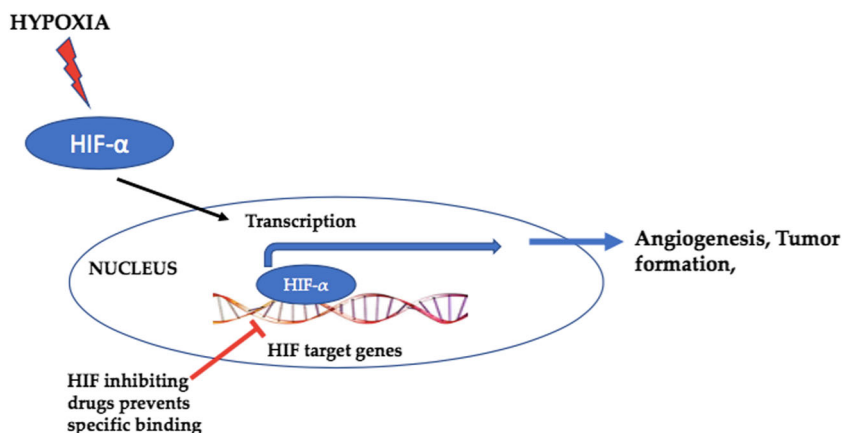
marine compounds as Topoisomerase inhibitors are listed in Table 3 and depicted by Fig. 11.

Wnt signaling inhibitors

Wnt signalling has been recognized as a regulator of cancer development and progression for more than 3 decades while these factors are active in numerous other contexts as well, for e.g. tissue homeostasis and embryogenesis [164]. Abnormal activation or aberrations in this pathway is involved in virtually all stages of oncogenesis eventually resulting in deteriorating anticancer immunity, a crucial contributor to tumor progression and eventual resistance to treatment [165, 166]. Recently inappropriate WNT signalling has been reported to destabilize the process of cancer immunosurveillance thus unfortunately facilitating resistance to immunotherapeutics and immunoevasion by directly altering plethora of regulators responsible for the antitumor activities of T cells, especially helper, regulatory and effector T cells [167, 168]. The distinctive feature of this signalling is the activation of β-catenin, the multitasking pivotal nuclear effector that acts both as a transcriptional co-regulator and as an adaptor protein for intracellular adhesion.
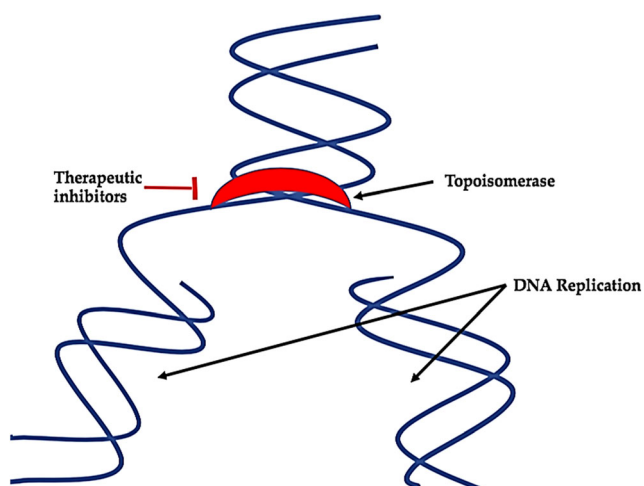

Fig. 11 Role of topoisomerase as a molecular target for cancer treatment

Wnt, a chief regulator of β-catenin belonging to a family of 19 glycoproteins. Interaction of Wnt ligands with frizzled receptor complexes can elicit numerous intracellular signalling cascades; which can be broadly divided into two types based on the involvement of transcriptional co-regulator β-catenin: In the first type of signalling i.e. β-catenin dependent (canonical) Wnt cascade, β-catenin is the core molecule that transduce the signal to the nucleus and triggers transcription of Wnt-target genes. Such genes are responsible for regulating cell fate decisions and plethora of other biological processes linked with progression of cancer for e.g. cell death, senescence & differentiation, tumor formation, proliferation its metastasis and tumor metabolism [169]. Interestingly, it has been documented that the canonical Wnt pathway facilitate cancer cells with a metabolically flexible environment by altering their metabolic activities as per their microenvironment and metabolic status. However, this pathway is itself regulated by the nutrients, enzymes and by-products of the metabolic pathway. Therefore, it signifies that Wnt/−catenin signalling represents a crucial target in the regulation of tumours metabolism. The second type of Wnt signalling known as independent (non-canonical) signalling is a collective term for numerous β-catenin independent pathways and comprises of Wnt/PCP (Planar Cell Polarity), WNT/Ca^{2+}, Wnt/PKC (protein kinase C) and various other pathways. Out of these reported noncanonical pathways, the Wnt/Ca^{2+}signaling pathway has been reported to be linked with tumor formation and progression [169]. Therefore, Wnt signalling could provide a brilliant target for the development of better cancer therapeutics. Some of the marine compounds as Wnt inhibitors are listed in Table 3 and depicted by Fig. 12.

Restraints of marine inhabiting invertebrates as Foundation for Anti-Cancerous Agents

The usage of biologically active composites of unexplored oceanic world as an alternative natural source will be increasing in the upcoming years for the invention of new drugs.

Fig. 12 Wnt pathway as a target for cancer treatment
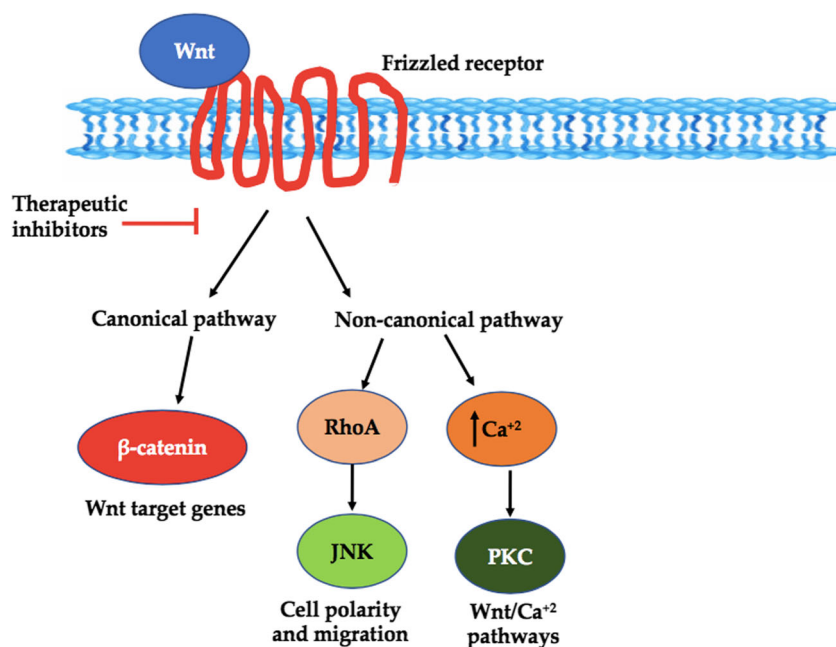
Nonetheless, some restrictions in the form of challenges cannot be overlooked:

- Supply problem and target identification.
- Scarcity of adequate quantity of natural product.
- Complications in retrieving the foundation of the samples, isolation and purification procedures.
- Complications linked with ingathering of the product.
- Difficulties in manufacturing the required quantities of the compound.
- Excessive toxicity of the effective compound.
- Unavoidable Inorganic salts resultant from the creatures or milieu.
- Comprehensive variety of chemical composites formed by a creature.
- Presence of indistinct pharmacological focusses.
- Ecological concerns.
- Government policies.
- Shortage of infrastructure and inadequate principal investment.

Inspite of drastic progress in the field of biomedicine and marine science, still there is scarcity of marine products that have paved their way to the marketplace. Variety of marine microorganisms are challenging to culture because of the unfeasibility in mimicking the drastic oceanic conditions. Moreover, scarcity of text on the sequestration techniques and standardized culture circumstances makes the condition even worse. Still it is of concern that very less numbers of academics are experts and undertaking such analyses. Cancer has been a disease since ages but till date lack of understanding of cancer biomarkers, the complexity of cancer genomics & proteomics pose a pronounced confront for marine anticancer drug investigation. There is an essential prerequisite for integrative and cooperative efforts so that innovated ideas can find their way to research organizations and being translated into new treatments. Lack of ample funding and infrastructure reserves to conduct the advanced clinical testing needed for regulatory approval of a drug, pose an impediment to the marine antitumor medication research. The vast structural diversity of marine natural compounds makes it challenging for the sequestration and refinement of these compounds and the progress of innovative anticancer drugs from these natural bases in contrast to synthetic compounds. Furthermore, prevailing extortions to worldwide marine biodiversity comprising habitat thrashing, overfishing, pollutants, rising water temperatures due to global warming and ocean acidification are building marine anticancer drug investigation increasingly difficult. These issues demand to be resolved for effective drug development of these drugs.

Contending downsides

Advances in technologies such as high-throughput screening approaches, usage of computational biology and bioinformatics, sampling approaches, nanoscale NMR for structure determination, development of synthetic or semisynthetic analogues derivatives and genetic engineering are altogether central to journey of marine natural products to become drug leads. As using these technologies we can produce compounds that are more efficient and have lower toxic, customized or undesired effects [170–174].

The issue of supply problem can be overwhelmed using an amalgamation of new methods in chemical synthesis and refining yield, aquaculture or isolation procedures [175]. Additional regulating aspect in the usage of marine creatures is the probable occurrence of toxic contaminants. Analytical procedures are presently available for the segregation, categorization and separation of effective compounds from marine extracts [176, 177]. Using controlled aquaculture techniques, we could escape the setback of fatiguing the marine assets and can generate the necessitated biomass for the high scale manufacture. To resolve the obstacle of identifying the molecular targets of the newly discovered MNPs, high-throughput screening procedures in conjunction with Omics (proteomics, genomics & metabolomics) and computer-generated screening have huge influence on the documentation of novel antitumor targets. The comparatively emerging fields of pharmacogenomics and pharmacogenetics should be integrated to overcome the limitations.

Conclusion

Increasing environmental abuses continue to intensify the frequencies of cancer with a challenge to find a cure with no or low side effects. Natural derivatives play an important role to check the cancer occurrences as an alternative source with low side effects and additional benefits. Drugs derived from marine biologicals have an enormous influence on antitumor drug discovery regimen of the existing day, nonetheless immense majority of oceanic habitation is underexplored in anticancer drug discovery due to numerous issues. This publication reviews the most newly sequestered, synthetically achieved or derived compounds/chemical constituents from oceanic environment (fauna & flora) that have displayed potential as cancer therapies with their mechanism of action as updated so far.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical issues This study does not involve any animal study or clinical trial itself, hence no ethical issues.

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