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Marine biome-derived secondary metabolites, a class of promising antineoplastic agents: A Systematic Review on their Classification, Mechanism of Action and Future Perspectives

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Abstract

Cancer is one of the most deadly diseases on the planet. Over the past decades, numerous antineoplastic compounds have been discovered from natural resources such as medicinal plants and marine species as part of multiple drug discovery initiatives. Notably, several marine flora (e.g. *Ascophyllum nodosum*, *Sargassum thunbergii*) have been identified as a rich source for novel cytotoxic compounds of different chemical

forms. Despite the availability of enormous chemically enhanced new resources, the anticancer potential of marine flora and fauna has received little attention. Interestingly, numerous marine-derived secondary metabolites (e.g., Cytarabine, Trabectedin) have exhibited anticancer effects in preclinical cancer models. Most of the anticancer drugs obtained from marine sources stimulated apoptotic signal transduction pathways in cancer cells, such as the intrinsic and extrinsic pathways. This review highlights the sources of different cytotoxic secondary metabolites obtained from marine bacteria, algae, fungi, invertebrates, and vertebrates. Furthermore, this review provides a comprehensive overview of the utilisation of numerous marine-derived cytotoxic compounds as anticancer drugs, as well as their modes of action (e.g., molecular target). Finally, it also discusses the future prospects of marine-derived drug developments and their constraints.

Keywords: Anticancer agents; Apoptosis; Drug discovery; Marine Microorganisms; Marine-derived products; Secondary metabolites.

1. Introduction

Cancer is a frightening heterogeneous malignant disease rising due to transforming habits, diet and global warming. According to Nogueira et al., 2020, climate change and global warming will severely impact people worldwide, with rising temperatures and the poor air quality being accompanied by higher rates of cancer, particularly lung, skin, and gastrointestinal cancers. Up to 2020, 19.2 million new cancer cases and 9.95 million deaths were reported worldwide, according to the World Health Organization (WHO) reports. Also, it has been anticipated that over 28.9 million new cancer cases and 16.2 million deaths may occur by 2040 (Ferlay et al., 2021). Although the cancer mortality rate constitutes about 13% of all deaths globally, it was suggested that altering or avoiding key risk factors can prevent more than 30% of cancer deaths (Smith and Oeffinger, 2020). The global market for cancer

medicines was estimated to be worth around 135.5 billion dollars in 2020. This market is expected to reach a value of 274 billion dollars by 2030. Between 2009 and 2020, there were 332 new anticancer approvals, including 209 (63 %) for a next-in-class indication in a new tumor type or a subsequent indication of the same medication in the same tumor type. When each tumor type was considered separately, 123 approvals (37%) were based on a novel mechanism of action (Olivier et al., 2021). Interestingly, products of natural origin and their derivatives account for more than 50% of the world's medicinal products in clinical use (Liu et al., 2019). Higher plants contribute about a quarter of the total, and nearly 60% of medications certified for treating cancer are found in nature (Abu-Izneid et al., 2020).

Recent advancements suggest that curing cancer is feasible in the early stage with the use of biochemicals, immunotherapy and modern drugs. For instance, human carcinomas like lymphomas (Atallah-Yunes et al., 2020), testicular cancer (de Vries et al., 2020; Lubberts et al., 2020), and childhood lymphoblastic leukemia (Balliot et al., 2019) had an improved clinical outcome with longer patient survival. Despite the significant advancements in current cancer therapies, chemotherapy leads to several side effects, limiting their use in the clinic. The search continues to identify newer promising treatment with lesser adverse effects (Vibala et al., 2020). Around 87% of human diseases, including cancer, have been treated with natural compounds (Alami Merrouni and Elachouri, 2021). Several reviews, like the updated survey from Newman and Cragg, (2016), pointed to the fact that many drugs on the market are from natural origin; these authors stated that, out of the 1,328 new chemical entities approved as drugs between 1981 and 2016, only 359 were purely of synthetic origin. From the remaining ones, 326 were “biological” entities (peptides of more than 50 residues, including therapeutic antibodies), and 94 were vaccines. A little less than half of those new drugs (549, exactly) were from natural origin or derived inspired from natural compounds. Furthermore, in the anticancer area, out of the 136 approved non biological compounds from

the same period (1981–2014), only 23 were purely synthetic (*i.e.*, not derived from natural compounds nor natural compounds themselves. These natural bioactive compounds often act via regulating major molecular signal transduction pathways such as nuclear factor (NF)-κB, extracellular signal-regulated kinase (ERK), and G protein-coupled receptor (GPCR) pathways were implicated in growth and progression of cancer (Zielińska and Katanaev, 2019).

In recent years, there has been a steady increase in the discovery of innovative anticancer drugs, with the US Food and Drug Administration (FDA) / European Agency for the Evaluation of Medicinal Products (EMEA) approving between 5 and 10 new anticancer treatments each year (Alves et al., 2018a). Altretamine is a synthetic alkylating agent of the methylmelamine class. Alkylating agents modify and crosslink DNA, inhibiting DNA, RNA, and protein production, and killing rapidly dividing cells. Bendamustine is a new alkylating agent with purine analogue characteristics (Harries and Gore, 2002). Bendamustine appears to be particularly effective against B-cell leukemias. Temozolomide, like dacarbazine, is an imidazotetrazine derivative that acts as an alkylating agent, interrupting DNA replication, modifying and cross linking DNA, slowing DNA, RNA, and protein synthesis, and triggering apoptosis in fast dividing cells (Farris et al., 2019). In clinical trials, temozolomide readily crosses the blood-brain barrier and shown to shrink malignant astrocytomas and Glioblastoma. Oxaliplatin is a cisplatin analogue with a tetravalent platinum molecule. To impede DNA, RNA, and protein synthesis and promote programmed cell death, It is currently used to treat colorectal cancer, usually in conjunction with 5-fluorouracil (5-FU), irinotecan, or capecitabine (Tong et al., 2021). Pralatrexate is a folate analogue that inhibits folate dependent enzymes like thymidine synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase. The drop in intracellular thymidine and purine concentrations prevents RNA and DNA synthesis and causes apoptotic cell death in rapidly

proliferating cells (O'Connor et al., 2021). Azacitidine is a pyrimidine analogue (5-azacytidine) that is converted intracellularly to a triphosphate and integrated into RNA and DNA. In solid tumours and lymphomas, azacitidine is an effective anticancer agent (El Fakih et al., 2018). Belinostat is a small chemical inhibitor of histone deacetylase that prevents acetyl group removal from histones. Acrylation of histones induces cell cycle arrest and apoptosis. Histone deacetylase inhibition is highly vulnerable to the impacts of malignant T cells (Goey et al., 2016). Bexarotene is a synthetic retinoid analogue and antineoplastic drug that regulates genes involved in cell differentiation and proliferation. Retinoic acid receptors (RARs) impact cellular development and proliferation, while retinoid X receptors (RXRs) often contribute to malignant cell death (Puri et al., 2021). Cabazitaxel is a semisynthetic derivative of a natural taxoid containing an 8-membered taxane ring. Activating intracellular microtubulin, which hinders the breakdown of cytoskeletal microtubules, prevents cell division, and causes cell death (Mout et al., 2021). Trifluridine is made up of an antineoplastic pyrimidine analogue (2-deoxy-5-trifluoromethyl uridine) and a thymidine phosphorylase inhibitor that slows down metabolism. Oral intake of trifluridine results in intracellular triphosphate formation, which inhibits DNA synthesis, slows cell growth and proliferation, and causes death (Weiss et al., 2022). Abemaciclib is an orally available, small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6 that is used in combination with fulvestrant in the therapy of postmenopausal women with metastatic breast cancer (Goetz et al., 2017). Sorafenib is a multikinase inhibitor that acts by inhibiting tumor growth by disrupting tumor microvasculature through antiproliferative effects. The multiple molecular targets of sorafenib, which include serine/threonine kinase (Raf), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor signalling in the clinical activity in Hepatocellular carcinoma (Peck-Radosavljevic, 2014). Majorly all synthetic anticancer drugs cause some degree of hepatotoxicity, and the liver

damage is mainly caused by direct, intrinsic toxicity. These drugs are effective but have adverse effects such as nephrotoxicity, cardiotoxicity, neurotoxicity, arrhythmias, electrocardiographic abnormalities, and myocarditis (Kim et al., 2021).

Due to the severity of toxicity with synthetic chemotherapeutic agents several human cancers considered as untreated (Ntie-Kang and Svozil, 2020). The marine domain has an unmatched potential for the discovery of new anticancer drugs and is an extremely useful tool for clinical trial in cancer cell differentiation. Anticancer drugs and natural products produced from marine sources are widely employed in the treatment of cancer and cancer related illnesses. They can also revive therapeutic agents derived from these drugs, such as natural immune agents, cytotoxic drugs, or chemical complexes. Most anticancer pharmaceutical markets rely on natural resources and engineered metabolites, which include mixes generated from marine species. Marine natural products have a variety of bioactivities that are pharmaceutically relevant (Nigam et al., 2019). Marine bacteria and fungus, as well as sponges, algae, and corals, have been demonstrated to produce novel secondary metabolites (SMs) with various chemical structures that can be used to develop anticancer treatments. Prokaryotes, notably marine bacteria like Lactobacilli and *Noctiluca scintillans*, algae (seaweeds) that produce secondary anticancer compounds. Similarly, marine microflora and microalgae make about 90% of all marine biomass. Many bioactivities have been documented that elicit MNPs, suggesting MNPs may be a rich source of new cancer treatments or therapeutic approaches (Alves and Diederich, 2021)**.**

In pre-clinical models and clinical studies, large numbers of marine chemical compounds serve as antitumor agents by effective inhibition of human tumor cell growth (de Vries et al., 2020). Cytarabine is a pyrimidine nucleoside isolated from the sponge *Tethya crypta*. Trabectedin is a tetrahydroisoquinoline alkaloid that was the first anticancer drug from the marine tunicate species *Ecteinascidia turbinata* to be approved in the EU for the treatment of

soft-tissue sarcoma and relapsed instances of platinum-sensitive ovarian cancer (Casagrande et al., 2021). Eribulin is a natural mitotic inhibitor identified in a marine sponge species (*Halichondria okadai*). Eribulin attaches to the developing ends of microtubules causing tubulin clumps and apoptotic cell death. Eribulin was licenced for cancer treatment in 2010 for metastatic breast cancer after anthracycline and taxan chemotherapy failed (Tarasiuk et al., 2022).

This review highlights the sources of different cytotoxic secondary metabolites from aquatic bacteria, algae, fungi, invertebrates, and vertebrates. Furthermore, this review provides a detailed summary of the use of marine-derived cytotoxic compounds as anticancer agents and their mechanisms of action (e.g., molecular target).

2. Recent advancements in marine biotechnology reveal the potential for the establishment of novel anticancer compounds

Marine microorganisms, in particular the tiny single-cell phytoplankton, make up 90% of the overall biomass in the oceans. As alluded above, marine microorganisms are a rich source of a wide range of cytotoxic compounds; some of them reported to have medicinal value rendering marine microbes are as a critical source for novel drug development (Albarano et al., 2020). Marine microbial products (MMPs) can be successfully converted into drug molecules towards commercialization, it is demonstrated that marine products can be used as valuable alternative sources for the production of novel therapeutic agents in the pharmaceutical industry (Kumar and Adki, 2018). While bottlenecks impede the drug development process, significant progress has been made in recent years to resolve the potential issues/risks in marine microbial product research/development (**Fig 1**). The extraction of potentially beneficial marine compounds from natural resources was not always therapeutically reproducible. As a result, supplying MMP material is still a crucial problem that would influence the structure of the elucidation and preclude a comprehensive biological

analysis of MMPs (Radjasa et al., 2011).Currently, one third of aquaculture production operates in marine waters, and this industry is growing and going farther and farther into the sea (Froehlich et al., 2017). Mariculture reached 30.8 million tons in 2018, with 37.5% coming from global aquaculture production and Asia contributing up to 88.69% (72.8 million tons) (Ahmad et al., 2021). The main species were mainly high-value fish such as salmon, sea bass, sea bream, barramundi, and trout, as well as bivalve molluscs and seaweed (Ahmed and Thompson, 2019).

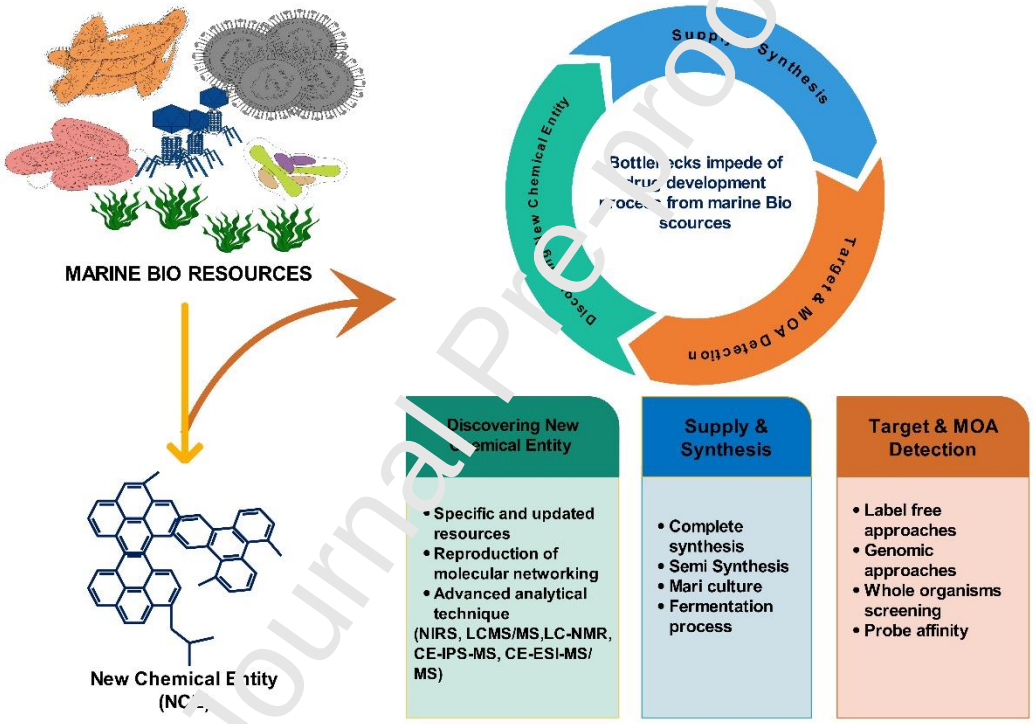

Fig 1. Three bottlenecks with its testing results highlight the exploration of marine natural drug spices.

A critical point in the process of drug development from marine organisms and often a bottleneck is the permanent availability of sufficient amounts of organisms and compounds without harming the marine environment. Only if sufficient supply may be addressed in an economically and ecologically feasible fashion, marine drugs having great economic value on the market (Rotter et al., 2021). If the collection of secondary metabolites from natural

environment cannot be operated in a sustainable matter, the supply problem can be solved by processes of marine biotechnology (aquaculture /agriculture /fermented cultivation; genetic engineering; enzymatic synthesis or modification) or by partial chemical synthesis/ semi synthesis/modification.

To meet commercial production needs, farming systems must be low-cost, simple to install, and maintain, with a small surface area to limit the risk of biofouling and instability. Until structure elucidation is completed, aquaculture remains a significant possibility to provide sustainable sources of marine animals and secondary metabolites (Maslin et al., 2021). Natural drug development is difficult due to the trace levels of natural substances contained in marine extracts, as well as the ecological and economic constraints that were addressed for the most part in this study. The construction of more sustainable and efficient supply mechanisms is still required to encourage and maintain current leads. Species with high yields of the required chemicals should be emphasized for study and selection since they do not require bulk collection to meet biomass requirements (Binnewerg et al., 2020). A realistic bioeconomic research of active molecules production based on the sponge model should be conducted for each compound in accordance with its current market pricing, if accessible. In the future, numerous opportunities to increase the appeal of sponge mariculture for drug discovery could be more thoroughly examined since it competes with in vitro alternative methodologies.

The prerequisite quality requirements for subsequent aquaculture exploitation must be met when producing in situ metabolites. The concentration of desired substances within the explants must then remain consistent or increase during the aquaculture process in order to maximize the value of natural populations. The proper commercial brood stock selection is critical, with donors exhibiting both rapid growth and high production rates for the secondary metabolites of interest. When trying to understand the changes in metabolites production of

explants throughout the year and between different habitats, continuous monitoring of microbial biochemical activity should be advocated. It can also be used to see if the explants' initial placement on the donor influences the following concentration of natural chemicals. Nonetheless, in other circumstances, a feasible drug development prospect is likely only possible if the projected quantities of ingredients are tiny enough to be reached (Maslin et al., 2021).

Despite the fact that MMPs are outstanding initial points in the advancement of pharmacotherapeutics, analysing biocompatibility and elucidating the fundamental process for converting it through effective biomedical applications remains a significant challenge. (Malve, 2016). Conversely, these techniques need intensive work to establish effective assay, perform Structure-Activity Relationship (SAR) evaluations, enhance biological structures of substance, and evaluate the findings, which are likely to be fake optimistic targets (Zheng et al., 2020). To rectify the issues as mentioned above, various label-free and genomic approaches have now been established to test the molecular target of different molecules, despite chemical alteration, in a high throughput manner (Schenone et al., 2013).

Label-free approaches include (i) Developed drug affinity responsive target stability (DARTS) to define molecular targets for tiny-molecules by analysing the interactions between protein-ligand, (ii) Cellular thermal shift assay (CETSA) to analyse the drug targeting. Here the biophysical principle of thermal stabilization triggered by the ligand of specific protein corresponds to a thermal shift in the melting curve into a higher temperature (Friman, 2020); (iii) Thermal stability shift-based fluorescence difference in 2D gel electrophoresis (TS-FITGE) is another label-free approach for defining a proteome-wide scale (Park et al., 2019); (iv) Stability of proteins from rates of oxidation (SPROX) utilized to determine the protein thermodynamic stability transition to classify targets by mass spectrometry (Li and Chen, 2019); (v) Size-exclusion chromatography for target

identification (SECTID) - this technique identifies the targets of small-molecule, which helps to minimize the issues with interactions of drug-target proteins (Goyon et al., 2018). The detailed label-free approaches in marine anticancer target development are depicted in **Fig 2 and Fig 3**.

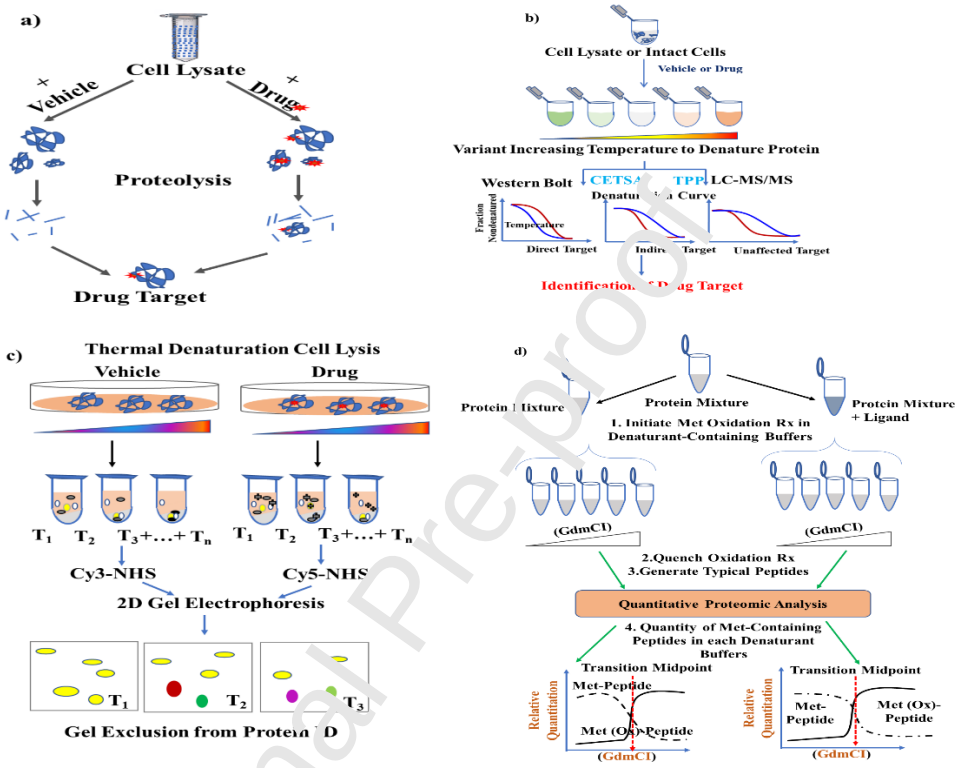

Fig 2: Schematic illustrations of label-free technology systems. **Fig. 2 a,** represents the proteolysis of drug affinity responsive target stability; **fig. 2 b** shows the identification of drug targets by cellular thermal shift assay; **fig. 2 c,** represents the fluorescent 2D gel electrophoresis based stable label-free approach and identification of drug targets; **fig. 2 d,** protein mixture containing legend processing with Met-Oxidation showing the rate of oxidation on the stability of the protein;

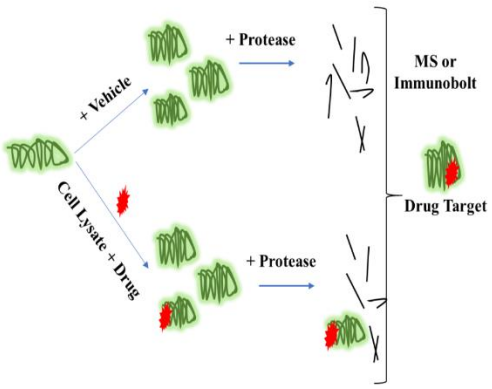

Fig 3. The steps involved in the target identification by size exclusion chromatography.

Recent genetic screening approaches such as the large-scale high-throughput gene disruption screening approaches have great potential in identifying targets of small molecules. This includes genome-wide loss- or gain-of-function genetic screens to identify the specific targets of potential marine natural products without any bias (**Fig 4**). In addition, the gene dosage evaluations that systematically modulate gene product levels through cDNA over expression as well as the siRNA-mediated mRNA suppression have been widely used to recognize the possible targets and mode of action of natural products (Haley and Roudnicky, 2020). Chromogenic profiling is another innovative genetic screening procedure that uses reduced or increased gene dosage for target identification. For instance, haploinsufficiency profiling (HIP) is a highly sensitive technique, which plays a critical role in defining the particular drug targets and pathways based on the reduction of gene copy numbers from two to one, that could improve drug sensitivity (Ulrich et al., 2020).

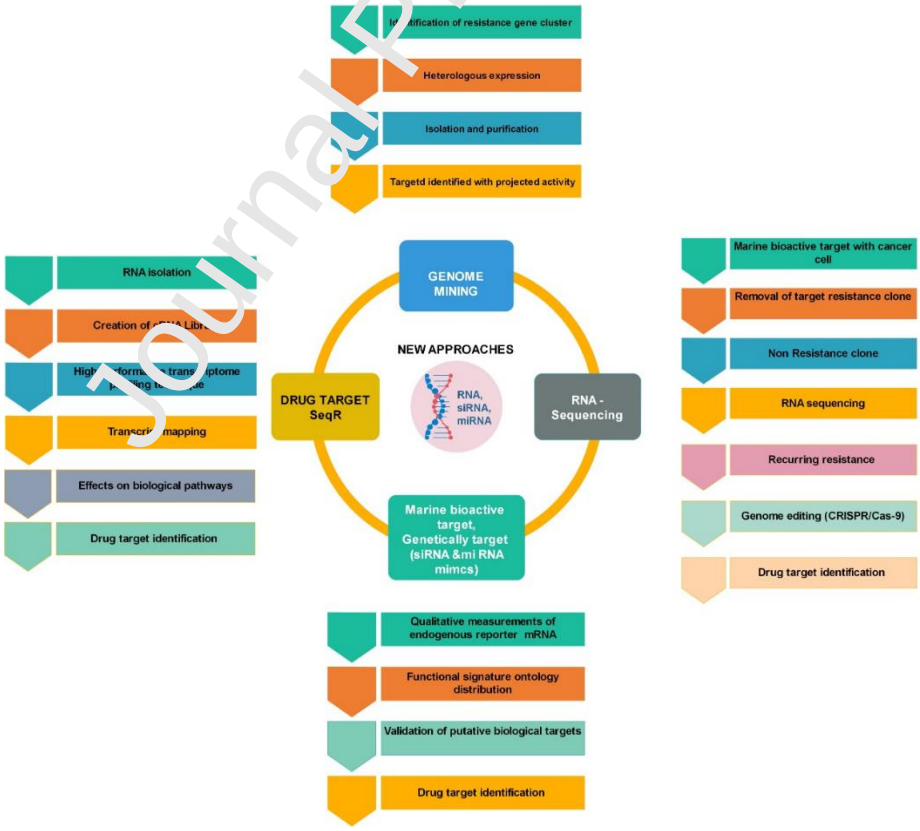

Fig 4. Strategies for the identification of the molecular targets of the marine microorganisms-derived anticancer agents.

Haploinsufficiency profiling is a timely and effective strategy, especially in light of recent studies that show that few medicines target single gene products (e.g. imatinib), providing an *in vivo* perspective of the relative sensitivity of all targets in the cell crucial for understanding the full mechanism of drug action. The HIP is based on discovering that a heterozygous deletion strain is sensitized to a drug that targets the heterozygous locus's product (as measured by a decrease in growth rate or fitness). When all feasible heterozygous deletion strains are evaluated simultaneously, the most sensitive heterozygous deletion strain frequently finds the drug targets. This test has the advantage of rapidly identifying the inhibitory drug and its prospective targets without the need for prior knowledge. In addition, these candidate targets indicate the most necessary genes for growth, making them helpful in identifying antiproliferative targets that could be used in antifungal or oncology applications. HIP screening well-characterized and novel drugs from marine sources revealed the feasibility and robustness of this assay (Wang and Peng, 2017).

A particular group of genes will exhibit a pattern of up-or down-regulation following the exposure to MMPs. These bioactive compounds are mainly produced by the activation of cryptic gene clusters, which are not active under normal conditions, and, thus, the expression of these clusters would be helpful in the exploitation of the chemical diversity of microorganisms. In addition, some biosynthetic genes stay silent and are not expressed *in vitro* (Singh et al., 2019). These signatures will be assembled in a matrix of similarity to create FUSION maps that connect the bioactive substances to unique biological processes (Xue et al., 2014). RNA sequencing (RNA-seq) has been considered as a high-throughput transcriptome profiling technique using the deep-sequencing methodology. It enables the identification of differentially expressed genes across the cellular signaling pathways and provides a key insight into numerous biological applications. Drug Target SeqR has been

designed to determine targets of drug molecules (Mun et al., 2020). The advantage of this technique is to know/determine the drug-sensitive/resistance gene mutations in cancer cells by high-throughput sequencing and to identify the therapeutic potential of the compounds of interest by combining CRISPR/Cas9-based genetic modification and combinatorial mutations (Mirza and Karim, 2019).

As described above, genetic screening for identifying biological targets has greater potential to discover the targets of MMPs. Comparable advances with the facilitation of marine organism/bacterial genome isolation act as a new approach for distinguishing natural products with biologically important compounds, chiefly antibiotics and anticancer drugs.

3. Specific marine sources of anticancer agents

3.1. Marine bacteria

Bioactive substances obtained from marine pseudomonas are diverse and include pyrroles, pseudo peptides, benzaldehyde, phenanthrene, pyrrolidinedione, andrimid, phenazine, quinoline, phloroglucinol, phthalate, moiramide, bushrin and zafrin (Gupta et al., 2013). Dibutyl phthalate and di-(2-Ethylhexyl) phthalate are recognized as cathepsin B inhibitors in several of these bioactive compounds. The most effective anticancer medicines produced primarily by marine bacteria include Bryostatin, Discodermolide, Eleutherobin, and Sarcodictyin (Singh et al., 2008). *In vivo*, Lactobacilli and *Noctiluca scintillans* demonstrated cancer-preventive activity against colorectal cancer and melanoma (Baindara and Mandal, 2020). Lactobacilli can minimize nitro-reductase and azo-reductase production. The diet of rats includes β-glucuronidase enzymes that help to decrease the typical level of intestinal enzymes, which suggests that Lactobacilli could reduce colon cancer incidence (Feyisetan et al., 2012; Nowak et al., 2019). *Bacillus laterosporus* produce the Basiliskamides A Anti-HeLa, Anti-HepG2, and cytotoxicity. Bacterial toxins are the most powerful cytotoxins produced by bacteria themselves. Cytolysin A (ClyA) is a bacterial enzyme toxin produced

by *Enterococcus faecalis*, which works by making pores in eukaryotic cell membranes and triggering caspase- mediated cell death. A few studies have found that treating mice with *Salmonella typhimurium* or *E coli* strains expressing the ClyA toxin inhibited tumor growth. They combined carbon nitride (C3N4) with an *E.coli* strain that was able to produce nitric oxide (NO). In a mouse model, the C3N4 loaded bacteria were accumulated throughout the tumor and the treatment resulted in a significant antitumor activity (~80% inhibition of tumor growth) (Sedighi et al., 2019). The marine-derived *Halomonas* spp, GWS-BW-H8hM strain, have been stated to prevent the development of HepG2 and gastric adenocarcinoma. The marine bacterium A5S-46 and strain ZZ338 from sea squirts is rich in actinomycin D, which triggers cell-cycle arrest leading to apoptosis in MCF7 cell lines and extensively inhibits the extra proliferation of human glioma U251 cells by down-regulating certain metabolic glioma enzymes from multiple metabolic pathways (El-Garawani et al., 2020). Extremely heterogeneous polymer composites, i.e. exopolysaccharides (EPSs) and sulphated EPSs extracted from *H. stenophila* showed pro-apoptotic effects on T-leukaemia cells in a hypersaline environment. Only the tumor cells are found to be more prone to the induction of oxidative stress by sulfate EPS (B100S), while T cells remain immune in nature (Asker et al., 2018). The isolated cytotoxic hydroxyl phenyl pyrrole dicarboxylic acids, from a marine *Halomonas* sp. i.e., 3,4-di-(4-hydroxy-phenyl) pyrrole-2,5-dicarboxylic acid (HPPD-2), 3-(4-hydroxyphenyl)-4-phenylpyrrole-2,5-dicarboxylic acid (HPPD-1), indole-3-carboxaldehyde, other indole derivatives 3-(hydroxyacetyl)-indole,indole-3-acetic acid, indole-3-carboxylic acid (Wang et al., 2006). Both HPPD-1 and HPPD-2 expressed potential anticancer activity by inhibiting 12-O-tetradecanoylphorbol-13-acetate (TPA) mediated early antigen facilitation of the Epstein-Barr virus. Bacterial metabolite Macrolactin-A has been reported to suppress B16-F10 murine melanoma cells (Regmi et al., 2015). A few potential active components of

bacterial isolates displaying possible anticancer and anti-proliferative activity are shown in **Table 1.**

Table 1: Some potential anticancer agents derived from marine bacteria.

Source	Compound structure	Clinical application
Cyanobacterium notostoc spp	Cryptophycins	Cytotoxic and anti-proliferative
Lyngbya Majuscule	Laxaphycin A	Cytotoxic effect on human lymphoblastic cells
Salinospora sp	Salinosporamide A	Antitumor activity (Human phase I clinical trials fo multiple myeloma)
Geitlerinema sp	Ankaraholide A	Antitumor activity on NCI-H-460 lung Tumor, breast carcinoma, and colon cancer
Lyngbya bouilloni	Apratoxin A	Anticancer potential on U2OS osteosarcoma, HT29 colon adenocarcinoma, and HeLa cervical carcinoma
Lyngbya majuscula	Aurilide B	Antitumor potential on human lung tumor
Nostoc sp.	Cryptophycin 1	Cytotoxic on Leukemia, Colon carcinoma, Mammary Carcinoma, Cervical carcinoma HeLa
Symploca sp.	Belamide A	Cytotoxic on HCT116 colon cancer
Lyngbya sp.	Bisebromoamide	Antitumor effect on HeLa S3 epithelial Carcinoma and lung cancer
Oscillatoria margaritifera	Ethyl tumonoate A	Anticancer on H-460 Lung Cancer
Symploca hydnoides	Malevamide D	Cytotoxic on lung cancer A549, colon cancer HT29 and melanoma MEL-28

Bacillus laterosporus	Basiliskamides A	Anti-HeLa, Anti-HepG2, and cytotoxicity

3.2. Marine fungi

In recent years, numerous categories of chemically distinct marine fungal metabolites have been reported with a wide variety of activities against several targets. Reviews have reported >1000 metabolites of marine fungi alone to have the potential to grow as drugs, with some as anticancer compounds, none of which have so far been on the market (Deshmukh et al., 2018). Nevertheless, for most of these results, the biological targets, full taxonomy studies, and way of interaction have not yet been established.

3.2.1. Deep-sea sediment fungi-based metabolites

Deep-sea fungi survive in the deepest part of 1000 meters or still more beneath the ground of extreme maritime environments, usually characterized by lack of sunshine, oligotrophic nature, lower temperature with higher hydrostatic pressure (Yuan et al., 2020). Some of the important bioactive compounds isolated from the deep-sea fungi have great anticancer potential, as displayed in **Fig 5**.

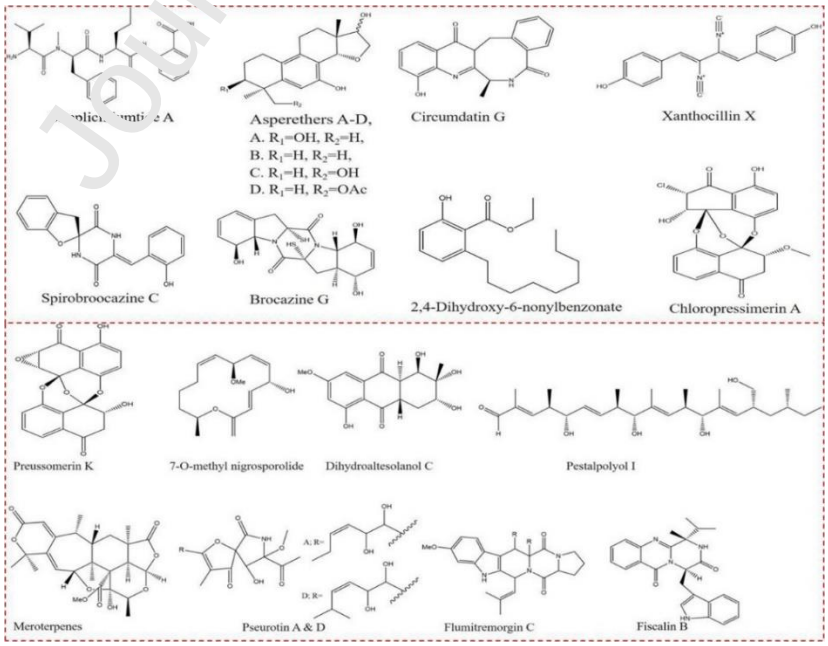

Fig 5. Deep-sea fungi sediment based anticancer medicine

The obtained linear peptide, simplicilliumtides A, from the broth of a deep-sea fungus, Simplicillium obclavatum EIODSF 020e, found in the east coastal part of the Indian ocean, is reported to have significant cytotoxicity against human leukemia HL-60 cell line with IC50 values of 64.7 μM (Liang et al., 2019). As per ethers A-D, five new 20-nor-isopimarane diterpenoids with a 14, 16-cyclic ether structure and unique 6/6/6/5 tetracyclic core skeleton, identified at the deep-sea sediment sample culture extract of *Aspergillus wentii* SD-310. The result showed powerful cytotoxic activity against the A549 cells, which was significantly higher when compared to positive control Adriamycin (Bladt et al., 2013). Circumdatin G collected from the deep-sea fungus culture *Aspergillus westerdijkiae* SSCIO 05233 showed anti-proliferative activities against K562 and promyelocytic HL-6 cell lines with IC_{50} values ranging between 25.8 and 44.9 μM. (Fan et al., 2018). Xanthocillin X has been shown to inhibit the growth of a variety of cancerous cell lines, MCF-7, HeLa, HepG2, MDA-MB-231, NCI-H460 and DU145 cell lines with the IC_{50} values of 12.0, 7.0, 10.0, 10.0, 8.0, and 8.0 μg/mL respectively (Zhao et al., 2012)

3.2.2. Potential anticancer molecules from mangrove endosymbiont fungi

The *Penicillium brocae* MA-231 obtained from mangrove endosymbiont fungi is rich in Spirobrocazines C and Brocazine G. The chemical configuration and total stereochemical nature of Spirobocazine C demonstrated restrained action on cells of A2780 (IC_{50} 59 μM). Brocazine G, on the contrary, exhibits incredible activity against A2780CisR cell and A2780, even greater than positive cisplatin performance with IC_{50} values of 6.64 and 6.61 μM, respectively (Meng et al., 2014). *Lasiodiplodia* sp obtained from *Excoecaria agallocha*, an endophytic fungus harvested from the mangrove, consists of the chief constituent 2,4-Dihydroxy-6-nonylbenzoate, which is cytotoxic to the MMQ and GH3 cell lines possessing IC_{50} values of 5.2 and 13.0 μM, respectively (Newman, 2018). *Lasiodiplodia theobromae* ZJ-

HQ1 endosymbiont fungus was extracted among the healthy *Acanthus ilicifolius* L leaf of marine mangrove. The Preussomerin H, Preussomerin G, Sprechzomerin K, and Preussomerin F are produced with two intact chlorinated preussomerin of this fungus and show better biological activity towards human cancer cell lines A549 and MCF-7 with low IC_{50} values ranging from 5.9 to 8.9 μM (Chen et al., 2016). 7-O-methylnigrosporolide obtained from mangrove resourced fungi *Pestalotiopsis* microspore showed the potential cytotoxic effect on lymphoma cells L5178Y, which showed lowest IC_{50} values of 3.9 μM (Liu et al., 2016). The Egyptian mangrove *Avicennia marina* plant was cultured for *Stemphylium globuliferum* and the extracted compounds of Altersolanols A, B, N, Dihydroaltersolanol C, and Alterporriol E showed greater toxicity to the L5178Y mouse lymphoma cell line with the IC_{50} values of, 3.7, and 6.9 μM respectively (Teiten et al., 2013). The mangrove fungi *Pestalotiopsis clavispora* isolated from the *Rhizophora harrisonii*, produced the fresh polyketide pestalopolyol I. It showed cytotoxicity against the mouse lymphoma cell line (Pérez Hemphill et al., 2016). Meroterpenes isolated from the *Penicillium* sp. marine fungus have a fundamental correlation to meroterpenoid miniolutelide and are classified as miniolutelide. The significant cytotoxic activity of Meroterpenes against human colon cancer cells HT-29 is by suppression and apoptosis of cell cycle by down regulation of ERK/JNK/AKT signaling pathways (Zbakh et al., 2020).

3.2.3. Marine deposit originated fungal compound

Deep marine soil-derived molecules isolated from *Aspergillus* sp resourced on the northeast coastal area of Brazil. Molecules such as fumitremorgin C alkaloids, 12, 13-dihydroxy fumitremorgin C, Hetero-spirocyclic γ-lactams Pseurotin A, and pseurotin D. All these compounds displayed potent toxicity to the HCT116 cancer cells with IC_{50} values 4.5 - 72.0, μM (Helal et al., 2019). Tryptoquivalin T, tryptoquivalin U, and fiscalin B isolated from *Neosartorya fischeri* have been shown to induce apoptosis towards the NCI-H460 and HCT -

1 cell line (Long et al., 2018). The bioactivity of compounds toward apoptosis of HL-60 cells were showed the IC_{50} values of 82.3, 90.0, and 8.8 μM respectively.

3.3. Anticancer potential of marine algae

Several experiments concentrate on aqueous soluble antitumor potent moieties from marine algae (**Table 2**). Until now, most anticancer moieties are not widely used because of their unintended harmful adverse effects on normal cells. Bioactive molecules destroy cancer cells by inducing apoptotic death or influence cell signalling by activating the protein kinase-C family of signaling enzymes (Lee et al., 2020).

Table 2: Some important anticancer compounds derived from marine algae.

Source	Active compound	Activity	Inhibitory concentration and cell line	Reference
Cyanobacteria				
Stigonema sp	Scytonemin	Protein serine Threonine kinase inhibitor antiproliferative	IC_{50} 0.08 to 10 μM Melanoma and spleen cells	Evans et al., (2021)
Cyanotoxins	Anatoxin-A microcystins/ nodularin	Treatment of Osteosarcoma	IC_{50} 0.08 to 10 μM NCI-H460 (human lung cancer)	Slizewska and Duda, (2021)
Calothrix sp.	Calothrixin	Anticancer	IC_{50} 5 pg/mL, KB Human nasopharyngeal cancer cells	Xu et al., (2016)
Aphanizomenon flosaquae	Aphanorphine, Siatoxin	Anticancer	IC_{50} 21.1 μM human fibroblast cell lines	Chermala et al., (2019)
Lyngbya majuscula	Microcolin-A	Immunomodulator	IC_{50} 6 nM –5.0 Mm, H-460 human lung cancer cells	Yu et al., (2019b)
Dinophyceae				
Poterioochromonas mathumensis	Malhamenicilipin-A	Inhibits the protein tyrosine kinase (PTK)	IC_{50} (62.8 ± 7.3 μg/mL HepG2 cells	Machana et al.,(2012)
Procentrum belizeanum	19–epi-Okadaic acid	A new protein phosphatase inhibitor	IC_{50} 1 nmol/L HeLa cell	Boopathy and Kathiresan, (2013)
Procentrum acuminate	Okadaic acid	Highly toxic against leukaemia cells by inhibiting	IC_{50} 0.1–1 ng/mL gastric cancer, colon cancer, PP2A	Campo et al., (2013)

		the enzymes of protein phosphatase 1 and 2A		
Amphidinium sp	Lingshioils A	Cytotoxicity	IC_{50} 4.13 µmol/L human lung cancer cell lines (A-549) and HL	Boopathy and Kathiresan, (2013)
Chlorophyceae				
Enteromorpha prolifera	Pheophytin	Suppressive effect against chemically induced mouse skin tumor genesis	IC_{50} 2.8 µg/ml U87MG cells	Cho et al., (2014)
Chlorella vulgaris	Oleic acid, linolenic acid, docosahexaenoic acid (DHA)	Immunomodulators	IC_{50} 20.2 µM, 17.8 µM and 16.5 µM, respectively, in DU-145 cells prostate cancer	Chrzanowska et al.,(2022)
Cladophora fascicularis	Porphyrinolactone	Inhibitory activity of NF-kB which is the origin of TNFa	IC_{50} 0.8 µM MCF-7 breast cancer cells	Mondal et al., (2020)
Avrainvillea nigricans	Nitric conoides A	Antimitotic activity for human breast cancer (MCF-7)	IC_{50} 4.67 ± 0.17 µg/µl, A549 cancer lung cells	Williams et al., (2007)
Cymopolia barbata	Cymobarbato	Potent antimitogenic properties	IC_{50} 19.82 µM MCF-7, HT29, HepG	Badal et al., (2012)
Bryopsis sp	Kahalaides	Phase II of clinical trials on breast and prostate tumours	IC_{50} 0.162–0.288 µM antitumor activity in colon	Kang et al., (2018)
Caulerpa sp.	Caulerpenyne	Anticancer, antitumor,	IC_{50} 21.2 µM , SK-N-SH cell line	Box et al., (2008)
Phaeophyceae				
Sargassum thunbergii	Fucoidans	Inhibiting tumour metastasis of rat mammary adenocarcinoma ells	IC_{50} 60, 63 and 211 µg/mL against MCF-7, WiDr and Vero Cells	Yudiati et al., (2016)
Halimeda stuposa	4-hydroxy dictyolactone	Human and mammalian colan cell lines	IC_{50} 1-5 µM against colon cancer cell line	Ovenden et al., (2012)

Stipodium zonales	Stypoquinoic acid	Inhibitor of tyrosine kinase and cytotoxic towards lung and colon cancers	IC_{50} 0.1–30 µg Colorectal adenocarcinoma	Moore et al., (2016)
Ascophyllum sp	Sulphated fucan, ascophyllan	Cytotoxicity	IC_{50} 12.6 µgmL−1 and 40.6 µgmL−1 against KB and HT-29 cells	Hussain et al., (2016)
Chondria sp	Condriamide-A	Cytotoxicity	IC_{50} 17 - 3000 ng/mL carcinoma cell line	Khalifa et al., (2019)
Rhodophyceae				
Chondrus ocellatus	λ-Carrageenans	Immunostimulant antitumour activity	IC_{50} 3.4 µg/mL Human osteosarcoma cellline	Liu et al., (2019)
Porteria hornemannii	Halomon	Strong cytotoxic action against several cancer cell lines	IC_{50} 20 and 42 µg/mL Sarcoma 180 MB-MDA-231, human breast-cancer cells	Tripathi et al., (2021b)
Gracillaria asiatica	Gracilarioside and gracilamides A and B	Strong cytotoxicity for the human melanoma cell line	IC_{50} 2.4 µg/ml Colorectal HCT 116 cells	S.S et al., (2017)
Laurencia filiformis	Preparguerene	Cytotoxicity on several cell lines (B16, HeLa, and P388)	IC_{50} 21.1 µM human fibroblast cell lines	Jongaramruong et al., (2002)
Laurencia obtusa	Teurilene	Cytotoxicity	IC_{50} 36.67 µM MGC-803 cell line	Güven et al., (2014)

Cyanotoxins such as microcystins/nodularine and anatoxin-A produced by Cyanobacteria, possess significant growth inhibitory potential against bone cancer (Zanchett and Oliveira-Filho, 2013). Lagunamides A and B are shown to have great effective cytotoxic cyclic depsipeptides, which are extracted from marine cyanobacterium filaments and *Lyngbya majuscula*. These have a similar structural analogy to aurilide type of compounds and they are considered to have an effective anti-proliferative effect upon cancerous cells U2OS, A549, BGC-823, HeLa, HepG2, MCF-7, BEL-7404, HL-60, HCT116, and A375 (Huang et al., 2016). Shanab et al. (2012) reported the growth inhibitory effect of segmented crude

extract of *Nostoc muscorum* and *Oscillatoria* spp, on Ehrlich's Ascites Carcinoma Cell (EACC) and HepG2 (Shanab et al., 2012). Scytonemin is a serum protein/threonine kinase inhibitor derived from *Stigonema* sp. Scytonemin, affects the development of mitotic spindles and the enzyme kinesis, which is involved in the cell cycle control (Itoh et al., 2013). Skitonemine acts as an ideal drug candidate because the protein kinase blockers of the molecule exhibit anti-inflammatory and anti-proliferative properties. Besides, this chemical substance inhibits the activation of human fibroblast and dendritic cells (Fan et al., 2019). The pentacyclic metabolites of indole (3, 2-) phenanthridine alkaloids and calothrixine A and B are known for its anticancer activity (X. Yang et al., 2019). It has been shown to exhibit better growth inhibitory effects against cancer cells A549 and NCI-H1650 at nanomolar concentrations. Microcolin-A, a lenient immune suppressive peptide eluted from *L. majuscula*, suppresses the double-way murine blended submicromolar lymphocyte reactivity. The other potent molecule, curacin A, has been identified from *Lyngbya majuscule* and shown to exhibit powerful anti-proliferative effects since it prevents polymerization of tubulin, which exhibits selectivity for breast, colon, and renal carcinoma cells (Yu et al., 2019). A most notable finding is the metabolite containing boron such as borophycin, along with cyanovirin, cryptophycins 1 and 8 extracted from *N. spongiaeforme* var. *tenue*, *Nostoc linckia*, and *Nostoc* spp marine cyanobacterial strains, and these bioactive molecules are notably cytotoxic against colorectal and epidermoid carcinoma of human (Eggen and Georg, 2002). The *Amphyprora alata* and *Ankistrodesmus gracilis* clearly show the most outstanding suppression of HepG2 cells (Tripathi et al., 2021).

3.3.1. Dinophyceae

Several species of dinoflagellates are capable of producing toxins. A few of these toxins remain very effective even in lower doses when compared to the standard chemical agents like camptothecin, doxorubicin, 5-fluorouracil, etc. Protein tyrosine kinase was shown to be

efficiently inhibited by Malhamenicilipin-A collected from *Poterioochromonas mathumensis* (Anand et al., 2018). For most of the species of *Procentrum*, Okadaic acid has been found to be present such as in *P. arenarium, P. maculosum, P. acuminate, P. concavum, P. fortii*, and *P. belizeanu*. Okadaic acid has incredible toxicity to leukaemia by inhibiting protein phosphatase (Fujiki et al., 2018). The 19–epi-Okadaic acid is a recent inhibitor of protein phosphatase extracted from *P. belizeanum* (Cruz et al., 2007). Dinochromes A and B are two carotenoids obtained from *Peridinium bipes* of aquatic species (Maoka et al., 2002). The anti-proliferative property of Dinochrome A has been revealed to be more effective over human cancer cell lines, like OST (osteosarcoma), HeLa (cervical cancer), and GOTO (neuroblastoma). The cytotoxicity effect of Lingshi oils A, obtained from *Amphidinium* sp., was observed against human lung cancer cell line A 549 and human myeloblastic leukemia cell line (Domínguez, 2013). Amphidinolide, another compound separated from *Amphidinium* sp., proves to have cytotoxic, antitumor, and antineoplastic activity by alkylation due to intercalation by topoisomerases through the deterioration of DNA (Bosch et al., 2019).

3.3.2. Chlorophyceae

Caulerpa microphysa extracts efficiently regulated human promyelocytic leukemia cells (HL-60, BCRC 60027). The report found that *C. microphysa* extract is rich in antioxidant and anti-proliferative activities on HeLa and Huh-7 cell lines (Tanna et al., 2020). The extracted chemical constituents of *Avrinvillea nigricans,* such as Nigriccanoides A and B have better antitumor action on MCF-7 and human colon cancer HCT-116 (Williams et al., 2007). *Cymopolia barbata* and *Neomeris annulata* rich in 4-isocymobarbatol and cymobarbatol are responsible for antimitogenic action (Barzkar et al., 2019).

Kahalalide, a linear and cyclic peptide extracted from molluscan species *Elysiya Rufscens* has reached a phase II clinical trial, verifying its effect on the prostate. These breast tumors

induce lysosome membrane disruption causing cell death (Shilabin and Hamann, 2011). Diarylheptanoids, such as cymodiene, cymodienol, nodosal, and isocymodine, separated from *Cymodocea nodosa*, together with another tricyclic diterpenebrominated, have more cytotoxicity to the NSCLC-N6 lung carcinoma cells (Kontiza et al., 2005). The caulerpenyne derived from the marine algal species of *Caulerpa* spp. has demonstrated its bioactivity against different human cancer cells (Tripathi et al., 2021). Meroterpenes and usneoidone have an antitumor function and these compounds are obtained from *Cystophora* spp. (Zbakh et al., 2020). Pheophytin, a Chlorophyll-based molecule derived from *Enteromorpha prolifera*, a versatile green microalga, has a definitive inhibitory effect over the rodent skin tumor model (Shailaja et al., 2019). In addition, very little research has been performed to explore the potential of anticancer and immunomodulatory properties of *Capsosiphon fulvescens* green algae, a Korean functional food for decades. *C. fulvescens* derived sulphated polysaccharide (SPS-CF) has a remarkable key immune-stimulating activity on murine RAW264.7 cells and apoptotic cell death human colon cancer cells HT-29 (Choi et al., 2019). The sulphated SPS-CF can synthesize pro-inflammatory mediators by stimulating macrophages to release IL-6, TNF-α, PGE2 and NO. This indicates the promising application of SPS-CF as an immunomodulatory agent in conjugation with anti-gastric cancer agents that were identified earlier (Manlusoc et al., 2019). The extracts from *Chlorella vulgaris* showed antitumor effects in animal studies. Apoptosis and oxidative degradation of HepG2 cells have also been reported for the *C. vulgaris* extract (A. Jayshree, 2016). The *C. vulgaris* microalgal species are often capable of developing antioxidants and anticancer medicine.

3.3.3. Phaeophyceae

The Fucales and Dictyotales are species of brown algae rich in secondary metabolites known to be useful in treating different cancer types. The medicinal texts from the Chinese and Ayurveda indicate that brown algae have been prescribed for the treatment of many cancer

types (Sanjeewa et al., 2018). Various extracts of seaweed (e.g. *Gelidium amansii*, *Laminaria japonica*, *Euchema cottonii*, and *Porphyra tenera*) were shown to suppress human gastric malignant growth (AGS) and colon-specific HT-29 tumour cells and mammary tumors on a dose-dependent basis (Usoltseva et al., 2019). The brown alga, Laminaria, has been indicated as a food supplement in breast cancer, which has a prevalence in approximately one-sixth of the women in Japan and US. The species of Sargassum and Laminaria have also been widely used as potential traditional cancer herbal remedies in China (Liu et al., 2012). Chinese and Japanese have long used the Laminaria, *Ecklonia* or *Undaria* as sources of iodine. The sulphated polysaccharides derived from *Saccharina japonica* brown algae and *Undaria pinnatifida* have successfully been screened against T-47D and SK-MEL-28 breast cancer cells for their antitumor activity (Gutiérrez-Rodríguez et al., 2018).

The major phytochemicals extracted from *Dictyota* sp and *Halimeda stuposa*, include diterpenes such as dictyol E, Xenicane diterpene 4-hydroxydictyolactone I, indole-3-carboxaldehyde and 8, 11-dihydroxypachydictyol A. The cytotoxic potential of these phytoconstituents has been reported against MCF-7, CHO-K1, SF-268, HT-29, and H460 mammalian and human cancer cell lines (El-Shaibany et al., 2020). Based on these reports, the majority of these isolated molecules showed nearly identical activity over the tested human tumor cell lines MCF-7, SF-268, and H460. *Sargassum oligocystum*'s water extract exhibits anticancer potential on human tumor cells, such as K562 and Daudi (Zandi et al., 2010). Some Sargassum species: S. fusiforme, S. confusum, S. lomentaria and S. kjellmanianum possess immunostimulatory competence in tumor-bearing rodent and apoptotic cytotoxic potential in selected human tumor cells (Sanjeewa et al., 2017). Brown seaweed algae-enriched fucoidans isolated from *U. pinnatifida* and *S. japonica* have extensively reduced both breast cancer and melanoma cell lines proliferation and colony formation in a dose-dependent manner. As reported by others, it has been proved that the

sulphated polysaccharides from *S. japonica* and *U. pinnatifida* are key elements for treating cancer (Malyarenko and Ermakova, 2017). The *Padina* spp hexane extract prohibits the growth of A-549 Lung carcinoma cancer cell lines by inhibition of topoisomerase I (Al-Enazi et al., 2018). As the extracts do not exhibit action against other cell lines, the activity of the extracts is called selective or unique as well as differential.

Extracts of *Ascophyllum nodosum* with low molecular weight fucoidan prevent human breast cancer cells infiltration by stopping them from binding to the extracellular matrix and restricting the penetration of colon adenocarcinoma cells (Anastyuk et al., 2012). Ascophyllan, a sulphated fucan, derived from *Ascophyllum* the brown algae has been studied against B16 melanoma cells for anti-metastatic activity (Abu et al., 2015). Moreover, the cytotoxic effect of polysaccharides has been reported only in Vero and XC cells, whereas it shows resistance to other cell lines.

3.3.4. Rhodophyceae

In red algae, there are ample secondary metabolites and halogenated derivatives. The antitumor activity of elatol and sesquiterpene isolated from *Laurencia microcladia* red alga was reported in Jurkat, Colo-205, U937, and B16F10 cell lines (Barcellos Marini et al., 2018). Also, Elatol's cytotoxic effect has been studied in C57Bl6 mice bearing B16F10 cells, where it induces apoptosis of cells by triggering growth inhibition in the G1 and sub-G1 stages (Campos et al., 2012). Western blot analysis indicates the appearance of cyclin-D1, cyclin-E, cyclin-dependent kinase (CDK) 2, and cdk4 gets decreased by the presence of elatol. A reduction in bcl-xl and a rise in the expression of bak, caspase-9, and p53 are similarly reported. Anti-proliferation activity has been documented in a human cervical adenocarcinoma cell line (HeLa) with ethanol extract from *Corallina pilulifera* calcareous red algae (Kwon et al., 2007). In another study, red seaweed *Acanthospora spicifera* showed tumoricidal activity in A549 cell lines. It was obvious as of the increase in average survival

time and the reduction in the number of tumors and cell viability counts. Oesophageal adenocarcinoma (EAC) is also controlled in implanted mice. The anti-proliferative activity of methanol, chloroform, and ethanol derivatives of *Enteromorpha lingulata* and Gracilaria edulis was evaluated in the HCT15 cell line (Murugan and Iyer, 2012).

3.4. Anticancer drug from invertebrates

Sponges of Porifera phylum, also known as "golf ball sponges or moon sponges", are said to be sessile marine invertebrates (Singh et al., 2021). *Cinachyrella* sp is primarily marine porifera with spherical or spiral body characteristics. Protein kinase C inhibition has been linked with joint pain and psoriasis pathogenesis and tumor development (Ruiz-Torres et al., 2017). Renieramycin M, which is a natural component derived from sponges, has shown to facilitate anticancer activity. In nature Renieramycin is a tetrahydroisoquinoline and it is a form of tetrahydro-quinoline (Pinkhien et al., 2016). In lung carcinomas, the apoptosis death of renieramycin M was due to the p53-subordinate apoptosis pathway (Rodrigo and Costa, 2019). Monanchocidin, a polycyclic guanidine alkaloid structure, is isolated from *Monanchora pulchra*, the marine sponge tested to produce cell apoptosis in human cervical mouse cells and human monocytic leukemia (Dyshlovoy et al., 2016). Spongistatin-I molecule separated from Spongia species induces severe cell death in several malignant cells by triggering growth arrest due to restriction of mitosis and increased attachment of vinblastine to tubulin fibrils (Xu et al., 2011). Heteronemin is another group of sponges examined in human cancer cell lines A549, ACHN, and A498 cells for its pharmacological effects to have antitumor activity (Wu et al., 2015). Heteronemin, a spongean sesterterpene affects cellular processes and also apoptotic cell death by TNFα-induced NF-κB signalling cascade due to inhibition of proteasome (Schumacher et al., 2010). Manzamine A exists in many of marine sponges also shows an antitumor effect (Gomes et al., 2016). The 8-hydroxymanzamine A is a Pachypellin species isolated from other types of sponge exhibits

mild antitumor and anti-herpes simplex virus-II activity (Samoylenko et al., 2009). *Sigmadocia pumila* and *Holothuria atra* (sea cucumber), the marine sponge's methanolic extract studied *in vitro* as well as *in vivo* experiments for the antitumor function. *S. pumila* and *H. atra* has retained a great level of antitumor activity towards human breast adenocarcinoma (MCF7), human breast ductal carcinoma cell (T47D), human cervix adenocarcinoma cell lines (HeLa), and human colorectal adenocarcinoma cell (WiDr) (Nursid et al., 2019).

In many regions of the world, mollusks such as oysters, clams, and abalone are considered delicacies. Bioactive peptides found in these organisms show antiproliferative and antimetastatic properties in cancer cells, including breast, prostate, lung, and colon malignancies. On the other hand, sea cucumber is a popular seafood delicacy in many Asian nations. It contains a number of triterpene glycosides and a variety of important amino acids and polyunsaturated fatty acids. When taken orally, frondanol A5, a glycolipid extract from the North Atlantic sea cucumber (*Cucumaria frondosa*), inhibited colon carcinogenesis in vitro and reduced colon cancers in animals. When taken as food, the anticancer activity of sea cucumber may be attributed to other chemicals rather than sulfated triterpene glycosides. Frondoside A, on the other hand, could be used as a lead compound in the creation of anticancer medicines. Therefore, the high-value compounds present in edible marine captures can pave the way for exploring their potential use for functional foods, nutraceuticals or even a new type of anticancer drugs (Correia-da-Silva et al., 2017)

3.5. Anticancer drugs from vertebrates

Tunicates, classified as Chordata phylum, belong to subphylum Tunicata or Urochordatais also known as urochordates, which has sac-like filter feeders with two syphons. Tunicate larvae display chordate features as they have a notochord, dorsal nerve, pharyngeal slit, and post-anal tail. In comparison, these tunicates often lack their tails and their potential to travel;

instead, they retain the vascular nervous system (Cooper and Yao, 2012). Several tunicates, often called as "sea squirts," live on the ocean's surface or on the sides of foreshore and ships. It has a strong cytotoxic effect across many cancer cell lines (**Table 3**). For example, dichloromethane extract of *Eudistoma vannamei* has important cytotoxic effects and it was evaluated in HL-60 promyeloblastic leukaemia cells, and results demonstrated that initiation of apoptosis in these cells, which proves the cytotoxicity activity (Jimenez et al., 2012).

Table 3: Summary of a few important clinical development and role of anticancer drugs extracted from the tunicate

Source	**Compound Name**	**Clinical Application**
Aplidium albicans	Plitidepsin	Phase III trials for Relapsed/ Refractory Myeloma in 2016
Ecteinascidia turbinate	Trabectedin	Ovarian cancer and Soft-tissue sarcomas treatment were approved by the FDA in 2015.
Lissoclinum sp	Hatenamaimide J	Cytotoxicity to P388 leukaemia cells
Lissoclinum voeltzkowi Michaelso	Chlorolissoclimide	Antiproliferative effect on non-small-cell broncho-pulmonary carcinoma line NSCLC-N6.
Eudistoma sp.	Eilatin	Antiproliferative effect on chronic myeloid leukemia
Lissoclinum patella	Lissoclinolide	Antiproliferative and cytotoxic effect on human colon carcinoma HCT116.
Aplidium Haouarianum	Haouamine A	Cytotoxic over the HT-29

		human colon carcinoma cell line
Botryllus Tuberatus	Tuberatolide A	Cytotoxicity towards several cancer cell lines.
Stolonica sp.	Stolonic acid A	Apoptosis activity in human and ovarian tumour cell lines.
Pycnoclavella Kottae	Kottamide D	Antimetabolic Activity, cytotoxicity towards tumor cell lines.
Synoicum Adareanum	Hyousterone A	Cytotoxic on numerous cancer cell lines.

As a result, these compounds also displayed anti-proliferative effects (Youssef et al., 2020). Also, the cytotoxic activity was studied for 7-alpha-hydroperoxy cholesterol and 7-beta hydroperoxy cholesterol (stereoisomer) of Formosan tunicate's lipophilic extracts in various cell lines (Jusakul et al., 2011). The cancer-defensive characteristics of 3-demethylubiquinone O2, includes disrupting cell transformation of JB6 Cl41 and p53 (vital tumor suppressor protein) and inducing apoptosis (Fedorov et al., 2008). AP-1 (a major transcription factor in multiple cancer-causing genes) and NF-Clβ activation (a protein complex) which is responsible for DNA transcription and is linked to cancer formation. New *Eudistoma gilboverde* N-methyl beta-carbon alkaloids showed different extents of cytotoxicity towards human cell lines (THP-1 cells, HL-60, and HT-460) (Rashid et al., 2001). Oda et al. (2007) have researched cytotoxicity of lissoclibadins and lissoclinotoxins from Lissoclinum cf. Badium, the tropical ascidian on nine different human cancer cell lines to test its future anticancer effectiveness. Anti-proliferative activity of dehydrodidemnin B

isolated from *Aplidium albicans* tunicate is through preventing the myc-oncogenic pathway. The results of the study suggest that its standard administration in Ehrlich carcinoma cultures decreases the total number of tumor cells by 70–90 % (Taraboletti et al., 2004).

3.6. Isolation technique of secondary metabolites from marine sources

Isolation and cultivation a new marine microbe could be a quick way to find new marine natural products (MNPs). It is difficult to culture all microbes from marine microenvironments. The majority of microorganisms from the environment (> 99.9%) do not form colonies on the nutrient-rich agar medium that has been utilized to isolate marine bacteria in the past. As a result, it is necessary to set specific, achievable, and relevant cultivation goals. A greater effort has been made to isolate the most-wanted or affluential from the marine resource. As stated by Paul Carini, key bacterial players may include those that (1) have a high relative abundance, (2) play key role in biogeochemistry or bioremediation, (3) have the potential to produce natural products, and (4) substantially diverge from cultured taxa (Mohamed et al., 2021). Although the simulated environment method has been a successful approach for isolating marine bacteria, especially for dominant species, with specific limitations as natural environments do not commonly have the optimum conditions for the growth of most bacteria.

The secondary metabolite extraction from different marine sources requires a distinct process each time. Researchers are using different methods to cultivate and harvest metabolites but combining them yields a novel technique. It is possible to isolate particular stains and perform early growth by inoculating and employing a culture medium with the seabed or seawater microorganisms and using the PCR technique to isolate DNAs for microorganism identification (**Fig 6**). Incubation and bioreactor/fermentation are used to cultivate metabolite production, and then chemical extraction and purification are performed. Different analytical

procedures, such as HPLC, NMR, LCMS, and MS, are used to isolate and identify the molecule (Bitzer et al., 2006; Du et al., 2010).

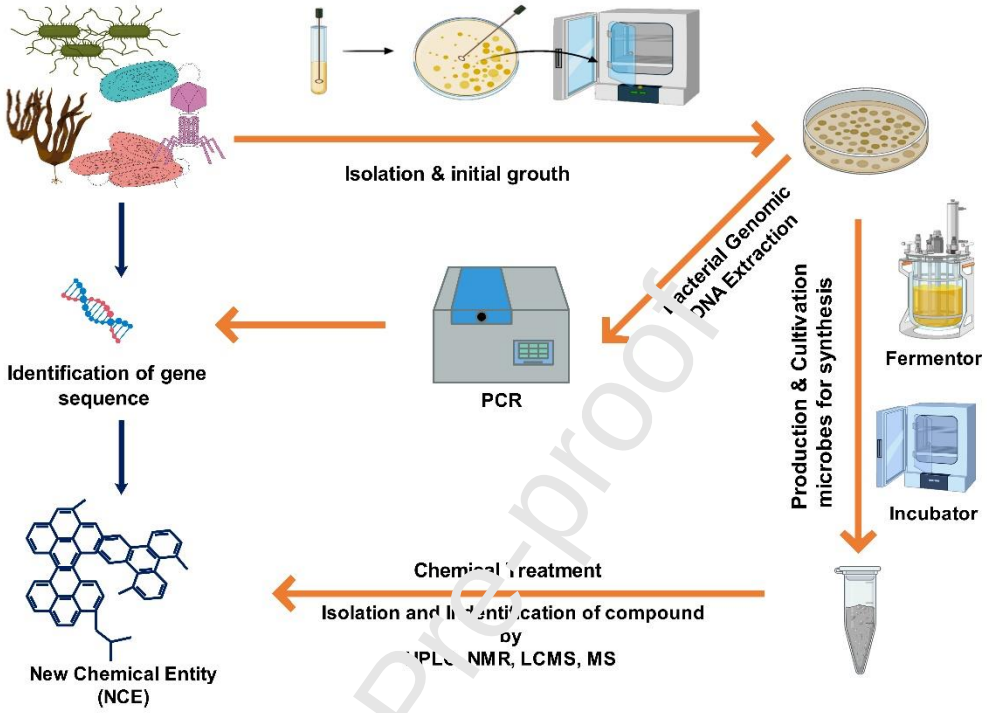

Fig 6. Schematic representation of isolation of metabolite from marine bio-scours.

Maintaining and modifying this technique provides a vital isolation approach; for example, Du et al. (2010) isolated four novel alkaloids from the deep ocean sediment-derived fungus *Penicillium sp.* - meleagrin D, meleagrin E, roquefortine H, and roquefortine I. They fermented the strain in a seawater-based culture medium, followed by chemical treatments and isolation and identification of metabolites using HPLC, NMR, and UV. Similarly, Sekar et al. (2015) isolated a non-toxic natural anticancer drug for lung cancer from *Candida albicans*, a marine yeast. The yeast was grown on agar media, isolated, and structurally elucidated using GC-MS, NMR, and XRD. The docking investigation using lung cancer protein revealed positive action. Also, Wang et al. performed yet another biosynthetic extraction investigation. The bioactive hydroxyl-phenyl-pyrrole-dicarboxylic acids were generated by the marine *Halomonas sp.* strain GWS-BW-H8hM. The microorganisms were

isolated from seawater samples and cultured in synthetic seawater. Further cultivation was carried out in order to extract metabolites from the microbe using the fermenter, followed by chemical treatment, isolation, and elucidation using several analytical techniques. Raji cells exhibit positive cytotoxicity toward inhibition (Wang et al., 2006).

Regardless of how the technology develops, culturing and isolating uncultured bacteria remains a time-consuming and laborious task. Thus, the most-wanted microbial groups in marine environments should be cultured first. A deeper understanding of the biogeochemical cycles mediated by microorganisms in marine environments requires better knowledge about the unculturable majority of bacteria, their relationships with coexisting members of the microbial community, and how they can be integrated as key players in biogeochemical processes. Importantly, the 'reverse genomics' approach should be considered for targeted culturing of key players (Cross et al., 2019). With this method, antibodies against predicted membrane proteins can be used to target and culture microbial cells from a specific taxonomic group. However, the efficiency of methods for isolating uncultured microbes from environments that harbor more complicated microbiota should be further explored.

4. Challenges in developing anticancer drugs from marine microbial sources

There are a few significant challenges and risks in developing drug molecules from marine resources. The presence of multiple secondary metabolites from the same organism could be due to complex environmental conditions. The most incredible difficulty often faced is that microorganisms that live in marine animals, marine hosts, and invertebrates actually produce bioactive molecules (Liu et al., 2017). A reliable isolated supply and established novel lead molecules often present a challenge, as the lead molecule is found only in a limited volume and is practically quite challenging to isolate (Elissawy et al., 2021). The candidate compound's lack of sustainable provision has often hindered several important marine novel compounds from further research and drug development. Numerous initiatives have been

produced in current years to overcome the above-mentioned obstacles by inventing synthetic or hemi-synthetic analogs with the preferred and optimized characteristics or developing a lower-complex pharmacophore and a more straightforward synthetic process. The detection of a bioactive compound synthesized or hemi-synthesized must also be rendered by comparison to a blend obtained from a natural source (Wali et al., 2019). The complicated structure of the isolated compounds and their poor yield, typically associated with marine compounds, can relate to an inappropriate allocation of the chemical compound formula and incorrect assignment of one or more stereocenters (Pham et al., 2019). For instance, the production of marine species in their natural environment through Mariculture and Aquaculture can also be promoted. A few things must be discussed at the early in the development process: (i) The future industrial application of the marine product and the need for that specific application of the compound on the market, (ii) The total cost for production per kg of the overall bioactive compound, (iii) Determined formulation loaded bioactive marine molecule with its preferred mode of administration, (iv) The ideal way to hit the market of the developed marine product (Press et al., 2019).

Marine microorganisms need adapt to the physical, chemical, and biological conditions of the oceanic environment, as evidenced by their physiology and biochemical features. The diversity of marine habitats has acted as a driving force in the selection of bacteria and fungi, resulting in new adaptation strategies and the synthesis of new compounds. Secondary metabolite production can be affected by adaptations to marine conditions. Variable environmental factors may each time lead to the creation of distinct metabolites from the same organism (Pham et al., 2019). Marine monohydroxy sterols present a wider diversity than those from terrestrial sources, given a large number of substitutions and rearrangements, leading to a vast array of side chains. Some marine microorganisms, namely microalgae and

fungus, were shown to change the sterol concentrations to respond to environmental stimuli (De Carvalho and Fernandes, 2010).

The successive drug development process includes the SAR relationship, highlighting medicinal chemistry advancement, formulation development, *in-vitro*, and *in-vivo* tests in animal models (Lindequist, 2016). Marine-derived anticancer drugs have the macrocyclic nucleic include four main subclasses according to their structural differences, namely, cyclic depsipeptides, diterpenes, macrolides, and macrocyclic alkaloids. The macrocyclic nucleic compounds have been reported from different sources, including algae, fungi, mollusks, cyanobacteria, sponges and gorgonians (Althagbi et al., 2020). The unprecedented skeletons of macrocyclic nucleic and structural complexity have an important role in the potency of their bioactivities. This has enhanced the discovery of anticancer drugs such as trabectedin, which is a tetrahydroisoquinoline alkaloidal derivative that the FDA has approved as an anticancer drug (Pereira et al., 2019). The structurally-related minor-groove alkylators trabectedin and lurbinectedin share a complex pleiotropic anticancer mechanism, affecting the tumor cells and the tumor microenvironment. Differing from conventional alkylators, both agents bind to the exocyclic amino group of guanines, with preference for guanine-cytosine-rich triplets of the DNA minor groove, causing an atypical bending toward the major groove (Jiménez et al., 2020). Consequently, a cascade of synergistic events is catalyzed, leading to an arrest of proliferation, differentiation, and cell death. In addition to the binding moiety, another subunit protrudes from the DNA backbone, interacting directly and indirectly with different DNA-binding proteins, such as transcription factors or DNA repair proteins (X. Yang et al., 2019).

The effective translation of MNPs into commercial pharmaceuticals highlights MNPs' potential as viable leads for therapeutic agent development. However, whatever the use of the molecule (drug, cosmetic, etc.), several grams to hundreds of grams are required for

preclinical research, multiple kilograms are necessary for clinical phases, and tones are required for cosmetic applications (Liang et al., 2019). The highest concentrations of toxic or deterring sponge metabolites are found in ecosystems such as coral reefs, which are characterized by intense competition and feeding pressure. This difficulty can be made considerably more difficult in the case of tissues from marine invertebrates, which present specific extraction-related issues due to their high water and salt content (Chen, 2021). In general, marine microorganisms such as cyanobacteria, algae, and fungus were acceptable for cultivation; nevertheless, the chemical of interest may need to be isolated and purified from specimens collected in the marine environment is challenging (Rotter et al., 2021). These limits result in the loss of a significant amount of accessible marine biodiversity and represent a significant bottleneck in the long-term supply of the required natural chemical.

The total synthesis, especially large-scale synthesis of complex MNPs, has provided plentiful material supply and valid chemistry evidence for a thorough biological investigation to promote the MNP research. For instance, the large-scale total synthesis of largazole, a class I histone deacetylase inhibitor found in marine cyanobacteria *Caldora penicillata*, was established, and the target compound's decagrams were obtained final product in 21% overall yield over eight steps (Chen et al., 2018). Apart from the approaches mentioned above, fermentation is also applied to provide MNP supply for scientific research and clinical investigations. Although the proteasome inhibitor salinosporamide A has been synthesized, its ongoing clinical investigations mainly rely on large-scale saline fermentation for continuous supply. Mohinudeen et al., 2021 produced higher yields produced camptothecin of up to 426.7µg/g and 403.3 µg/g dry weights from *Alternaria alstroemeriae* (NCIM1408) and *Alternaria burnsii* (NCIM1409), respectively, using a simple laboratory fermentation process. In a jar fermentation procedure, wild-type Streptomyces sp. in the batch technique produced 205 mg of piceatannol from 342 mg of resveratrol in 20 h (Roh and Kang, 2014).

5. Mechanism of action of marine microorganisms-derived anticancer therapeutics

In response to anticancer treatments, apoptosis is an effective cell death process as a form of cellular signaling/metabolism (Beesoo et al., 2014). Cell death is vital for growth, physiology, and homeostasis. Since apoptosis typically does not induce an allergic or immune reaction, apoptotic cancer cell death is desirable for treating cancer. This apoptotic pathway regulation and selective apoptosis activation with the natural compound are usually the more effective route to cancer therapy (Mudit and El Sayed, 2016). The induction of apoptosis caused by the numerous activating caspases, a group of enzymes that functions as cell damage-trigger compounds in many modes of apoptosis, may be extrinsic or intrinsic **(Fig 7).**

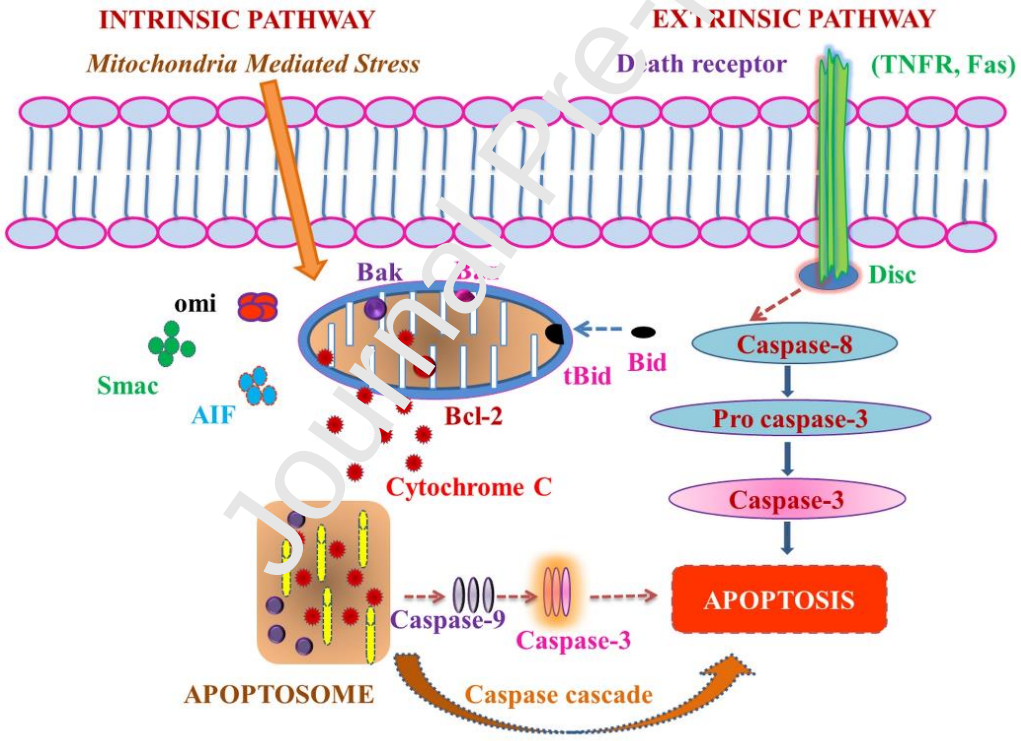

Fig 7. Extrinsic and intrinsic mechanism of apoptosis. The receptor-mediated-extrinsic or mitochondria-mediated-intrinsic signaling pathways can trigger apoptotic cell death in cancer.

5.1. Extrinsic pathway

The extrinsic mechanism of apoptotic cell death is triggered on the cell surface by the binding of a particular ligand to its associated cell membrane negative regulator. Death receptors (e.g., Tumor necrosis factor receptor [TNFR], TNF-related apoptosis-inducing ligand [TRAIL] receptor, and Fas) belong to the TNFR super family (Wajant and Siegmund, 2019). Upon binding of a ligand (e.g., TNF, TRAIL, and FasL, sequentially), the death receptors aggregate in plasma mucosa and enable adapter protein recruiting (Schneider-Brachert et al., 2013). Caspase 8 Zymogen can link with the adapter proteins (e.g., FADD and RIP1) to create the active component of Caspase 8 to activate the downstream action of Caspase 3, which cuts the protein function that leads to apoptosis (Salvesen and Walsh, 2014).

5.2. Intrinsic pathway

The intrinsic death impulses, e.g., reactive oxygen (ROS), DNA damaging reactive, and Ca^{2+} mobilizing stimuli, stimulate the mitochondrial pathway directly or indirectly, leading to cytochrome C release and the production of the apoptosome complex containing cytochrome C, Apaf-1 and caspase-9 (Distrutti et al., 2016). The pro-apoptotic protein Bid assists like a cross-talker in binding the receptor and the mitochondrial signaling pathways after cleavage by caspase-8 activation through triggering the migration of Bax and Bak, the pro-apoptotic proteins, to promote permeabilization of the outer mitochondrial membrane. Therefore, Bid binds the receptor to the mitochondrial pathway and can activate its caspase proteolytic processing, leading to a mitochondrial amplification loop (Baig et al., 2016). Bcl-2 inhibition of Bax activation becomes a successful technique to activate an apoptotic mechanism (Naseri et al., 2015). Furthermore, caspases are involved in both intrinsic and extrinsic apoptosis pathways, so identifying caspase activators develops a new pathway towards discovering novel anticancer agents.

The signaling mechanism through PI3K/AKT (phosphatidylinositol 3- kinase / threonine-specific) plays a crucial part in several cellular activities. It prevents the PI3K/AKT signaling pathway has becoming an efficient technique for cancer therapy targeting (J. Yang et al., 2019). In addition, numerous drugs, for example, Apratoxin A, GV-c9, and GV-c1, LS-1, SD, have established critical anticancer features by hindering the JAK/STAT innate immune signaling pathway (Saeed et al., 2021). Therefore, bioactive natural aquatic products may have novel medicinal uses in preventing or treating cancer by modulating and enhancing physiological functions. A successful way to formulate newer anticancer agents is to isolate or produce these compounds, which attack several genes regulating apoptosis. Through various pathways, a large number of naturally occurring marine products with antitumor activity and that cause apoptosis have been identified over the past 20 years; apoptosis which of specific importance to us. Because of the presence of many extensive marine compounds, only MNPs and their synthesis variants that are in either clinical trials or successful test drugs that have influenced apoptotic pathways in tumour cells will be the priority of the research study.

6. Prospects of anticancer agents derived from marine sources

One of the most effective treatment strategies for cancer involves targeting various cellular signaling transduction pathways implicated in tumorigenesis. Some regulators of such mechanisms recently emerged and further research has been performed on marine organisms to balance tumor growth progression and diminish carcinogenesis. Modern anticancer drug research searches for potent cytotoxic compounds with improved performance, efficiency, and specificity (Malve, 2016). By the estimation available, promising anticancer molecules of marine origin are divided into various groups of chemicals, most of which are terpenes (40.5%), peptides (19%), macrolides (14.3%), and alkaloids (12%). In these, 50 % are considered anticancer agents for the first time. The bulk compounds found in vegetables and

berries are chemotherapeutic (92.7%), nutraceuticals (7.3 %) (Florean et al., 2020). The molecular mechanisms implicated in the anticancer effects of compounds under investigation are primarily cell cycle arrest by inhibiting the action of tubulin and various activation mechanisms of caspases 3, 8, 7, and 9 that induce apoptosis (Boice and Bouchier-Hayes, 2020), mitochondrial membrane potential depolarization (Aminzadeh-Gohari et al., 2020), Bcl xL, Bax and polymerase cleavages (ADP ribose). Anti-migratory effect by inhibitory behavior in specific, transient receptor potential cation membrane (TRPM -7) channels (Sarwar et al., 2018). Anti-angiogenic properties by restraining the secretion of vascular Endothelial Grown Factor A; anti-inflammatory function by suppressing the expression of COX 2 and iNOS (Alves et al., 2018b). The ability to classify active moieties of marine resources for targeted cancer therapy is not yet particularly effective due to the large ability of resources for potent therapeutic products

The discovery and development of novel therapeutics from natural products (NPs) have played an important role in the past few decades. NPs are responsible for around 28% of new chemical entities and 42% of anticancer drugs that have been introduced to the market. In addition to plants and animals, microorganisms are valuable for innovative drug development (Alves et al., 2018a). More than 50,000 microbial natural products (MNPs) have been obtained, and they have played an important role in the creation of medicines. The majority of these have been found in terrestrial microbes. Over 15,000 structurally distinct MMPs with a bewildering diversity of bioactivities have been found in marine settings since the 1970s (Rotter et al., 2021). Over the last two decades, more than 18,000 new marine compounds were described and the approval of more than 300 patents (Saeed et al., 2021). The FDA has approved six marine-derived therapeutics that are now being used in clinical applications, as well as one over-the-counter drug (OTC) (Alves et al., 2018a). However, with 28 marine or marine-derived pharmaceuticals currently in clinical trials (**Table 4**), it is

projected that the number of newly approved drugs from the sea will continue to rise (Khalifa et al., 2019). The nanobiotechnological sector is seeing an increase in the use of nanomaterials for the development of cancer drugs. MNPs could be a source of anticancer medication delivery systems. Nanoformulations are linked to a wide range of nanoparticles, and their polymerized structures are becoming a popular method for generating specialized cancer medicines (Bajpai et al., 2018).

Table 4: Marine-derived anticancer drugs approved or in clinical trials

Drug	**Source (marine organism)**	**Treatment**	**Progress status**	**Reference**
Brentuximab vedotin	Cyanobacteria *Dollabella auricularia*	Hodgkin lymphoma and chronic large cell anaplastic lymphoma	FDA approved in 2018	Saeed et al., (2021)
Cytarabine,	Sponge *Cryptotheca crypta*	Acute nonlymphoblastic leukemia	FDA approved in 2017	Saeed et al., (2021)
Eribulin mesylate	Sponge *Halichondria okadai*	Metastasized breast cancer	FDA approved in 2016	Saeed et al., (2021)
Trabectedin (Yondelis®)	Caribbean tunicate *Ecteinascidia turbinata*	Ovarian cancer; soft tissue sarcoma	FDA approved in 2015	Saeed et al., (2021)
Depatuxizumab mafodotin	Cyanobacterium *Caldora penicillata*	Adenocarcinoma and advanced solid tumors	Phase III	Pereira et al., (2019)
Enfortumab	Cyanobacterium *Caldora penicillata*	Progressive urothelial cancers	Phase III	Pereira et al., (2019)
Lurbinectedin	Tunicate *Ecteinascidia turbinata*	Ovarian cancer and small cell lung cancer	Phase III	Ning et al., 2018
Marizomib	Actinomycete	Multiple myeloma	Phase III	Saeed et

	Salinispora tropica	and glioblastoma		al., (2021)
Plinabulin	Marine fungus *Aspergillus sp*.	Neutropenia and Non-small cell lung cancer	Phase III	Saeed et al., (2021)
Polatuzumab	Cyanobacterium *Caldora penicillata*	Diffuse large B cell lymphoma	Phase III	Saeed et al., (2021)
Enzastaurin	Bacterium *Streptomyces staurosporeus*	Diffuse large B cell lymphoma; glioblastoma	Phase III	Saeed et al., (2021)
Aplidine, plitidepsin	Tunicate *Aplidium alpicans*	Multiple myeloma; precursor cell lymphoblastic leukemia lymphoma	Phase II	Wang et al., (2020)
Ladiratuzumab vedotin	Cyanobacterium *Caldora penicillata*	Breast cancer	Phase II	Wang et al., (2020)
PM060184	Sponge *Lithoplocamia lithistoides*	Breast cancer; colorectal cancer	Phase II	Wang et al., (2020)
Indusatumab	Cyanobacterium *Caldora penicillata*	Colorectal cancer; gastrointestinal cancer	Phase II	Wang et al., (2020)
Glembatumumab	Cyanobacterium *Caldora penicillata*	Brain cancer; Breast cancer; malignant melanoma;	Phase II	Pereira et al., (2019)
Midostaurin	Bacterium *Streptomyces staurosporeus*	Acute myeloid leukemia; systemic mastocytosis	Phase I	Wang et al., (2020)
Elisidepsin	Mollusc *Elysia rufescens*	Gastric cancer; nonsmall cell lung cancer	Phase I (suspends)	Wang et al., (2020)
Pinatuzumab	Cyanobacterium *Caldora penicillata*	Chronic lymphocytic leukemia; diffuse large	Phase I (discontinued)	Pereira et al., (2019)

		B cell lymphoma; nHL		
Lifastuzumab	Cyanobacterium *Caldora penicillata*	Fallopian tube cancer; non-small cell lung cancer; ovarian cancer; peritoneal cancer	Phase I (discontinued)	Newman and Cragg, (2020)
Vandortuzumab	Cyanobacterium *Caldora penicillata*	Prostate cancer	Phase I (discontinued)	Newman and Cragg, (2020)

In addition, Principe and Fisher recently evaluated a database of information on 298 pharmaceutical compounds derived from marine biota over the last 50 years. The products were created from 1,296 collections of specimens from 69 countries and all 7 continents, representing 232 different marine species belonging to 15 phyla. An analysis of the spatial distribution of sample collection locations yields a map showing where and when specimens with MNPs with pharmacological potential (for which clinical data is available) were gathered. The study's purpose was to find sites that provide MNPs with proven or potential usefulness rather than to have a representative sampling of chemical structures or geographic regions. This allowed researchers to identify the species from which the MNPs were separated and the locations where the specimens yielding those MNPs were gathered. Data from 1,296 specimen collections encompassed 298 MNPs (including 16 FDA-approved medications, 55 compounds under clinical development, 51 compounds in the preclinical investigation, and 176 lead compounds or probes) (Ntie-Kang and Svozil, 2020).

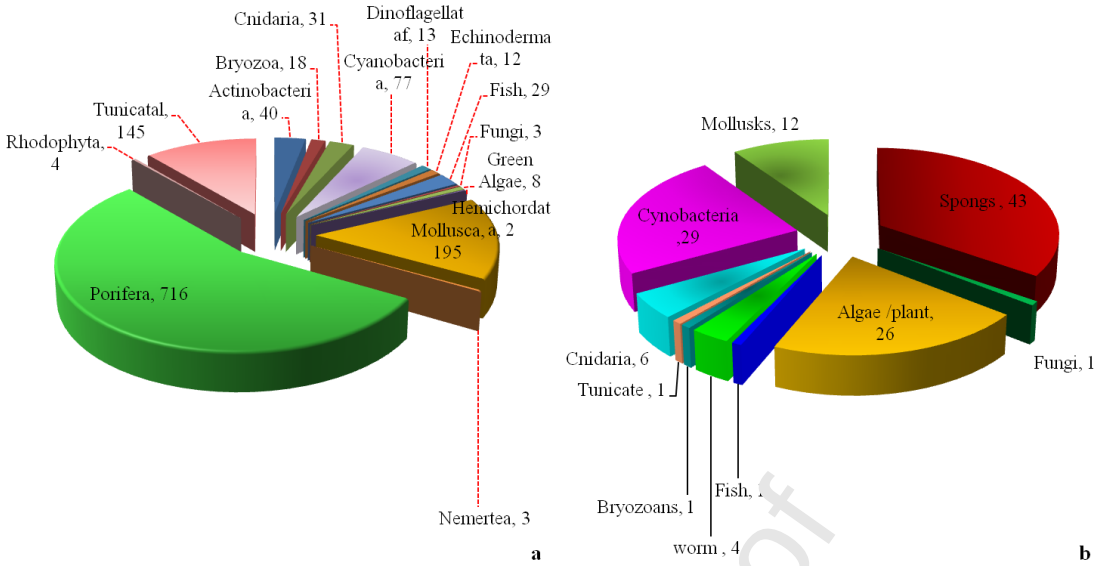

Fig. 8: (a) Pie chart illustrating comprehensive marine and terrestrial sources, **(b)** Pie chart illustrating the collected sources of marine natural products used as bioactive research products that are available commercially for their useful pharmacological properties in biomedical research (121 total).

Fig 8 represents the recent comprehensive marine and terrestrial sources, commercially bioactive products for their useful pharmacological properties in biomedical research.

7. Conclusion

As mentioned in brief, the marine environment has marvelous productive environment wherein new potential medicines are being hunted, particularly with new anticancer agents. It suggests that the incredible progress in developing new anticancer treatments has an extremely efficient marine ecosystem. It suggests that the extremely efficient nature of the marine ecosystem is responsible for this incredible progress in developing new anticancer treatments. However, it has the purpose of chemical defense from predation, overgrowth, or other types of competitive interactions. Thus, the exciting adage is that the difference between pharmaceutical products and toxins is a matter of dosages in this case. In addition, numerous marine drugs have established critical anticancer attributes by an extrinsic mechanism of apoptotic cell death via triggering death receptor pathway (TNFR, TRAIL, and

Fas) and the intrinsic or mitochondrial pathway (Caspase proteolytic processing, Bcl-2 inhibition Bax activation). The PI3K/AKT signaling pathway has also proven to be an effective strategy for therapeutic cancer targeting. For instance, meroterpene class anticancer drugs induce cell cycle apoptosis by inhibiting the ERK/JNK/AKT signaling pathways. Heteronemin affects cellular processes as well as apoptotic cell death via the TNFα-induced NF-κB cascade due to proteasome suppression. A further conclusion of this study is a high level of multidisciplinary and innovative activity that impregnates this research field. This eventually makes scientific research more exciting; it also encourages creativity and discovers new values and developments. The remarkable feature of these innovations has been born from one field and freshly and spontaneously introduced to another. Consequently, creating the MS2 molecular data networks can only be one of the milestones in pursuing marine microbes for their medicinal properties.

Abbreviations:

ADP: Adenosine diphosphate ribose, Akt: Protein kinase B, Bax: Bcl-2-Associated X protein, Bcl-xL: B-cell lymphoma extra-large, BEL: Cellosauarus cell line, Cas9: CRISPR associated protein, CHO-K1: Chinese hamster ovaries cell lines, Colo 205: Colon cancer cell lines, Cox-2: Cyclooxygenase-2, CRISPR: Clustered regularly interspaced short palindromic repeats, DU-145: Human prostate cancer cell line, ERK: Extracellular signal-regulated kinases, F-268 – Human glioma and astrocytoma cell lines, G1: Gap-1-phase, GH3: Pitutiary adenoma cell lines, HCT116: Human colorectal carcinoma cell line, HeLa: Human epithelial carcinoma cell line, HepG2: Human liver cancer cell line, HL: Human leukemia cell line, Huh7: Hepatocyte-derived carcinoma cell line, IL-6: Interleukin-6, iNOS: Inducible nitric oxide synthase, JNK: c-Jun N-terminal kinase, MCF-7: Breast cancer cell line, MDA-MB: Epithelial human breast cancer cell line, miRNA: Micro RNA, MMPs: Marine microbial products, MMQ: Rat pituitary prolactinoma cell line, MOA: Mode of action, NSCLC: Non-

small-cell lung carcinoma, RNA: Ribonucleic acid, siRNA: Small interfering RNA, SK-MEL-28: Human skin melanoma cell lines, THP-1: human acute monocytic leukemia cell line, TNFα: tumor necrosis factor alpha, TRPM7: Transient receptor potential melastatin 7, U-937 leukemia cell lines.

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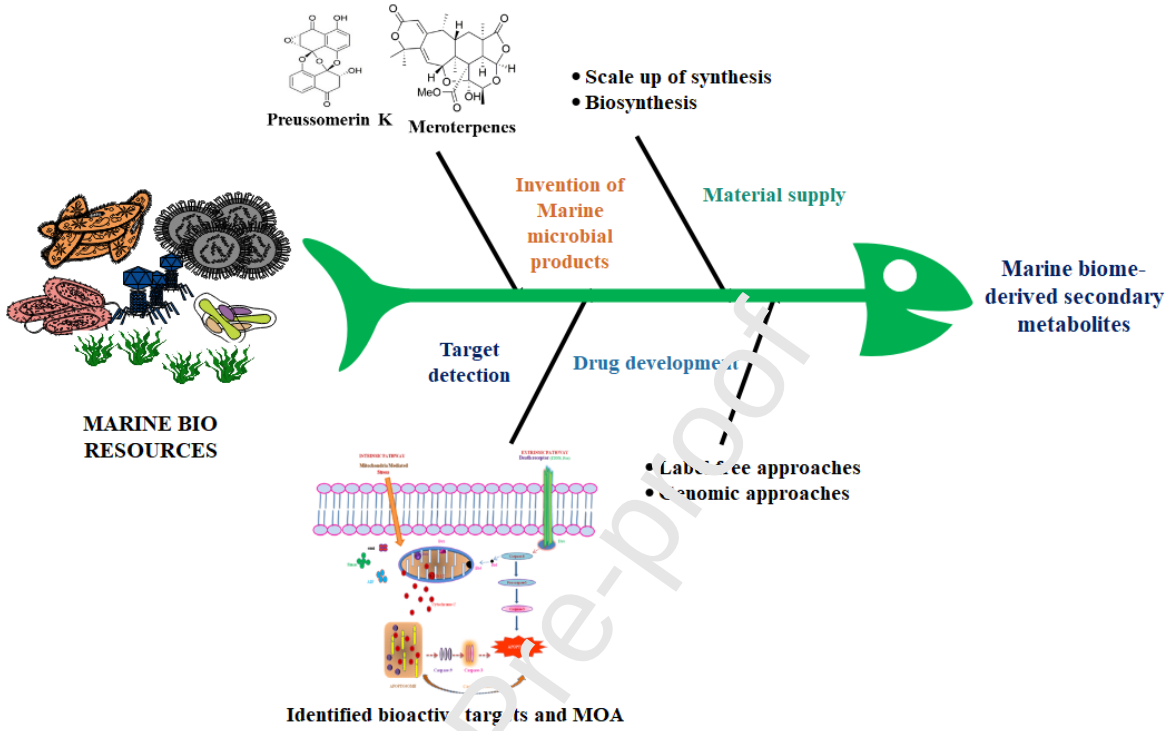
Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Graphical abstract



Highlights

- Marine-derived secondary metabolites reported having potent anticancer activity.
- Marine microorganisms are a prime source of novel anticancer drugs.
- The molecular targets of marine-derived cytotoxic compounds have been identified.
- Metabolites of marine origin are an example of important producers with therapeutic potential.