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Marine bacterial metabolites in anticancer drug discovery: Ecological insights, mechanisms of action, and clinical translation

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ABSTRACT

Marine ecosystems contain a pool of diversely chemical microorganisms with the ability of producing structurally unique bioactive metabolites. Bacteria derived in the sea have become a major source of innovative anticancer agents with particular activity and lower toxicity of the system. Recent findings have depicted the remarkable anticancer effects of marine bacterial metabolites, including Seriniquinone, Salinosporamide A, Didemnin B and Bryostatin analogues, which have a high level of cytotoxic, pro-apoptotic, and immunomodulatory effects on a wide range of aggressive and treatment-resistant cancers. Marine-based molecules are less likely to damage normal tissues as compared to conventional chemotherapeutic agents, have a high likelihood of attacking particular signalling pathways, mitochondria, proteasomes and redox homeostasis. This review explains the application of marine bacteria in anticancer drug discovery and highlights ecological features of marine bacteria, structural and functional variation of their secondary metabolites, and molecular pathways of their anticancer effects. These pathways are cell cycle arrest, regulation of intrinsic apoptotic pathway, autophagy, proteasome, and immune. The review also assesses the preclinical data and new translational data on the relevance of marine bacterial compounds in cancer treatment. It is also concerned with the issue of large-scale manufacturing, the complexity of biosynthesis, and clinical translation. As the field of marine microbiology, chemical biology, and cancer pharmacology evolves, additional studies of marine bacterial biodiversity, genomics, metabolomics, and synthetic biology are highly likely to result in the next generation of anticancer agents, resistance circumvention, and patient outcomes.

1. Introduction

One of the most important causes of morbidity and mortality in the world is cancer, which claims millions of lives per year even with the great progress in the field of its diagnosis, prevention, and treatment (Lin and Park, 2024; Saini et al., 2020). Based on the latest world statistics, the burden of cancer will continue to grow in the next few decades due to increase in population, age, change in lifestyle, and

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environmental influence. Despite increasing survival rates of various malignancies with the use of conventional therapeutic approaches, including surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy, their combined clinical success remains poor due to the presence of such challenges as drug resistance, systemic toxicity, tumor heterogeneity, and disease relapse. The above issues highlight the urgency in the discovery and development of new anticancer agents that have better efficacy, selectivity, and safety profiles(Advani et al., 2022; Aljabali et al., 2025).

Natural products have always been the focus in the discovery of anticancer drugs, either directly as agent or as model of synthetic and semi-synthetic derivatives. Classic examples like paclitaxel, doxorubicin, vincristine, bleomycin and Camptothein derivatives demonstrate the timeless role of natural products in oncology(Sarkar, 2023; Sofi and Tabassum, 2023). Such molecules frequently have complicated chemical scaffold structure, and novel action mechanisms that are challenging to achieve by entirely synthetic methods. Nonetheless, most naturally-derived anticancer drugs that have been successfully used in clinical practice are obtained by using terrestrial flora and microorganisms. The focus has been on marine ecosystems in recent years as a relatively unexploited source of biodiversity and chemical novelty of enormous therapeutic potential (Ahmed et al., 2022; Banday et al., 2024) (Fig. 1).

Marine ecosystems occupy over three-quarters of the total land area of the earth, and occupy an extensive spectrum of extreme and highly diverse ecological niches, such as deep-sea sediments, hydrothermal vents, Polar Regions, coral reefs, and symbiosis microhabitats around marine invertebrates. The microorganisms that live in these conditions have developed unique metabolic processes in an attempt to survive the conditions of high pressure, salinity, low temperature, low nutrients and extreme competition(Reineke and Schlömann, 2023; Singh et al., 2020). Consequently, marine microorganisms, in particular, marine bacteria, can synthesize structurally unique secondary metabolites with high biological activity. These metabolites are often shown to have novel modes of action, and are therefore very appealing target anticancer drugs, especially in terms of combating resistance to current drugs.

Marine bacteria have become an extremely fruitful and multipurpose source of anticancer bioactive compounds. Bacteria have a number of practical benefits (compared to marine macroorganisms) such as faster growth rates, genetic manipulability and the possibility of sustainable production using fermentation-based and synthetic biology-based methods. The development of marine microbiology, genomics, metabolomics, and bioinformatics have greatly increased the speed at which previously uncultivable or cryptic marine bacteria species and their cognate biosynthetic gene clusters have been identified(Jain and Tailor, 2020; Viju et al., 2021). This has resulted in the identification of many marine bacterial metabolites with strong cytotoxicity effect on a broad spectrum of malignant cell lines, such as malignant and treatment resistant ones.

Salinosporamide A, a highly active proteasome inhibitor based on the marine actinomycete Salinispora tropica, has been advanced into clinical trials in hematological malignancy, and is one of the most interesting examples(Manikkam et al., 2024; Seyed and Ayesha, 2021). In the same vein, Seriniquinone, the active constituent of a marine Serinicoccal species, has been shown to have selective anticancer activity due to its ability to act as a targeting agent against cancer-associated proteins and activity inducing apoptosis. Thiocoraline and didemnin derivatives, and other polyketides and nonribosomal peptides, are other interesting marine bacterial products, which also emphasize the excellent chemical and therapeutic diversity of marine bacterial metabolites(Carroll et al., 2020; El-Bondkly et al., 2021).

This is a distinguishing characteristic of most marine bacterial anticancer compounds that they regulate a series of essential cellular pathways that are aberrantly regulated in cancer. These comprise cell cycle arrest, induction of apoptosis, autophagy, inhibition of proteasomes, inhibition of mitochondrial functioning, redox deregulation and immune and inflammatory signaling mediations(Sadiq, 2023; Venditti and Di Meo, 2020). Notably, a number of marine-derived molecules have been found to have selective toxicity in cancer cells and sparing normal tissues, which is very desirable in the field of oncology. It has

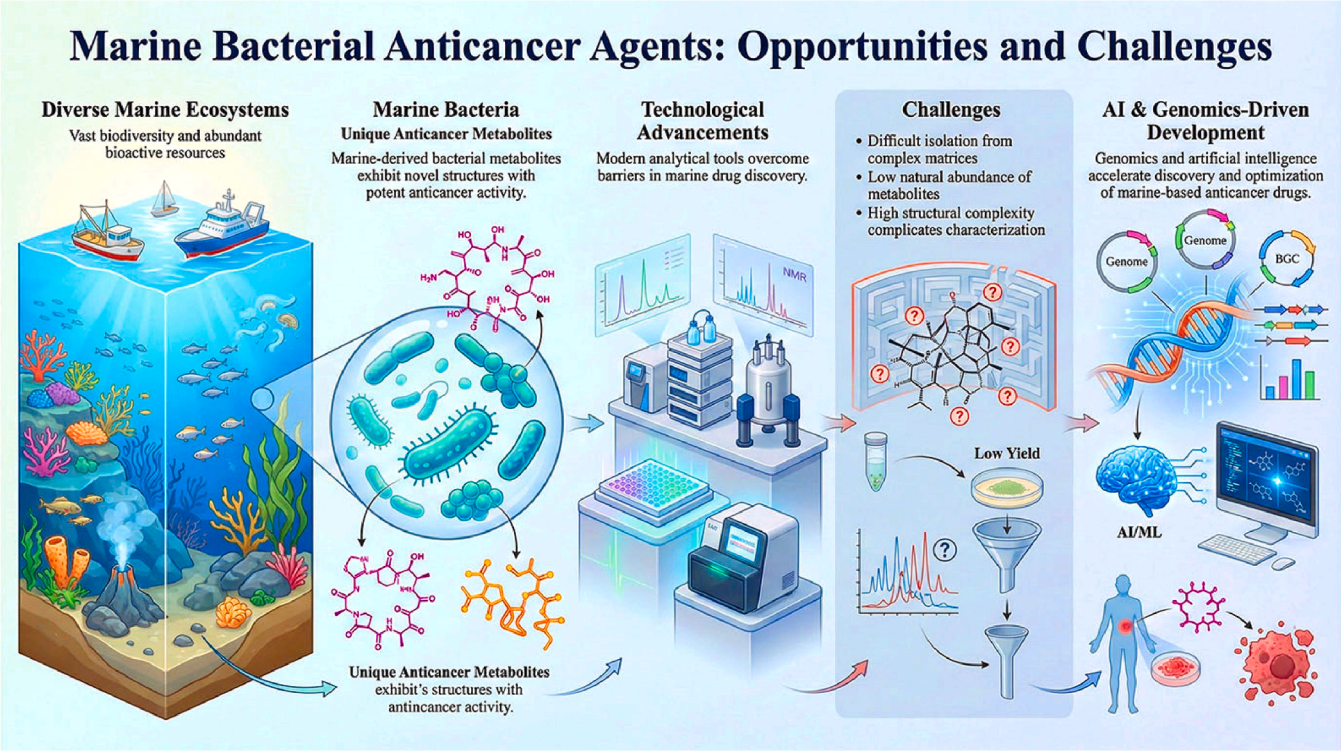

Fig. 1. This figure illustrates the opportunities and challenges in developing marine bacterial anticancer agents. It covers diverse marine ecosystems, unique metabolites from marine bacteria, technological advancements, challenges in isolation and low yield, and AI/genomics-driven development.

been speculated that such selectivity is caused by the targeting of cancer-specific metabolic dependencies or signaling weaknesses and lessens off-target effects typically related to conventional chemotherapeuticals.

Although these properties have come with these promising characteristics, many challenges hinder the translation of marine bacterial metabolites into anticancer drugs that are clinically approved(Santos et al., 2020; Wang et al., 2020). These encompass challenges in the isolation and provision of compounds, complexity in structure, which makes synthesis of the compounds difficult, inconsistency in the production of the metabolites, and poor knowledge on the pharmacokinetics and extended toxicity. Additionally, sampling, biodiversity conservation, and intellectual property rights are logistic and regulatory issues that are associated with the marine environment(Lionetto et al., 2021; Rogers et al., 2023). To overcome these challenges, the interdisciplinary collaboration involving marine biology, chemistry, pharmacology, synthetic biology, and scientific discovery platforms based on data is needed.

New technological development is starting to alleviate most of these constraints. With the help of genome mining and metagenomic methodology, identification of silent or cryptic biosynthetic gene clusters has been possible, indicating that there is a huge reservoir of unexplored potential anticancer compounds. Heterologous expression and optimization of biosynthetic pathways is possible using synthetic biology and metabolic engineering approaches to enable the production of complex marine bacterial metabolites in large amounts(Ng et al., 2020; Yang et al., 2022). Moreover, machine learning and artificial intelligence solutions are also being used to forecast bioactivity, lead optimization, and investigation of structure-activity relationships, simplifying the process of drug discovery.

Marine bacteria in this case would form a viable and biologically sustainable source of anticancer drugs(Batra et al., 2023; Santos et al., 2020). They are also the most chemically diverse to date, with improvements in technologies in analytical and computational methods, and are in the spotlight of the new generation of oncology therapeutics. The entire picture of the sources, structures, mechanisms, and translational potential of marine bacterial anticancer compounds is the key to the implementation of their clinical potential.

The review is an attempt to synthesize recent and detailed knowledge on the use of marine bacteria as a source of anticancer agents. Our areas of interest are the taxonomic variety of marine bacteria, the chemical families of their anticancer metabolites, and how they act in their therapeutic effects(Robles-Banuelos et al., 2022; Stonik et al., 2020). Furthermore, we critically appraise the evidence of preclinical and emerging translational, explain the primary challenges in drug development, and point out what can be done ahead of time to make marine bacterial compounds mainstream cancer therapy. The review attempts to highlight the potential of marine bacteria in oncology by bringing together knowledge of marine microbiology, chemical biology, and cancer pharmacology to elucidate the potential of a sea change in fulfilling unmet requirements in the field (Table 1).

2. Marine bacterial diversity and biosynthetic potential

The marine environments are one of the most heterogeneous and multifaceted ecosystems on the planet that includes a large range of physical, chemical, and biological factors(Chakraborty, 2023; Robles--Banuelos et al., 2022). These ecosystems support an exceptional number of microorganisms with marine bacteria being the key players of nutrient cycling, symbiosis, and ecological balance. In the superficial waters of the sea to deep-sea sediments and hydrothermal vents, the marine bacteria have developed extremely specialised metabolic functions to survive in the extreme environment of high salinity, high pressure, low temperature, low nutrient levels and strong levels of interspecies competition. These selection forces have facilitated the strategic development of distinctive biosynthetic pathways making the marine bacteria an abundant source of structurally differentiated and biologically powerful secondary metabolites with immense pharmacological applications, especially in oncology(Ahmad et al., 2025; Rui et al., 2025).

2.1. Marine habitats and microbial adaptation

Marine bacteria are found in a wide range of ecological niches and each of them places a unique selection pressure that determines the metabolism and the production of secondary metabolites in microbes. Piezophilic and psychrophilic bacteria grow in deep-sea, high hydrostatic pressure, low-temperature, and nonexistent sunlight environments and have the capability to yield metabolites with atypical structural characteristics and other bioactivities(Ahmad et al., 2025; Kanekar and Kanekar, 2022). In like manner, hypersaline habitats favour halophilic bacteria that produce osmoprotective and stress-response molecules with a significant proportion having cytotoxic or antiprolliferative characteristics. Hydrothermal vents and cold seeps are additional chemically enriched ecosystems, in which bacteria flourish with heavy metals, sulfides and intense temperatures gradients, usually producing new bioactive products(Cong et al., 2022).

Besides the free-living marine bacteria, symbiotic relationships with marine invertebrates, i.e., sponges, tunicates, mollusks, and corals, have received specific attention in anticancer drug discovery. In marine sponges specifically, they contain compact and heterogeneous consortia of microbes that can be 60-percent of their biomass (Dervash et al., 2023). It is assumed that these symbiotic bacteria have a defensive role in which they produce secondary metabolites that prevent predation, fouling and competition by other microbes of the host. It has since been found that many compounds initially ascribed to marine invertebrates are due to their microbial symbionts, and hence the significance of microbial contribution to marine chemicals.

Competitive marine ecosystem adaptation has also facilitated development of chemical warfare practises by bacteria culminating in

Table 1
This table summarizes the key factors influencing marine bacterial anticancer agent development, including marine ecosystems, bacterial metabolites, therapeutic properties, challenges in isolation, and technological advancements that support drug discovery and production.

Marine Ecosystems	Marine Microorganisms	Secondary Metabolites	Anticancer Properties	Challenges	Technological Solutions
Vast and diverse	Bacteria, fungi, algae	Proteasome inhibitors, polyketides	Apoptosis induction, cell cycle arrest	Isolation difficulties	Genome mining, metagenomics
Deep-sea, hydrothermal	Actinomycetes, Bacillus	Nonribosomal peptides	Targeting cancer proteins	Structural complexity	Synthetic biology, fermentation
Coral reefs, Polar Regions	Symbiotic bacteria	Polyketides, thiocoraline	Selective cytotoxicity	Inconsistent production	Metabolic engineering
Microhabitats around invertebrates	Marine Serinicoccal species	Seriniquinone, didemnin	Immune signaling, redox regulation	Limited pharmacokinetics knowledge	AI-driven lead optimization
Extreme conditions (pressure, salinity)	Marine bacteria species	Redox-active compounds	Apoptosis and autophagy	Regulatory and conservation issues	Heterologous expression
Vast unexplored biodiversity	Marine-derived compounds	Broad spectrum of activities	Inhibition of mitochondrial functioning	Intellectual property concerns	Machine learning for bioactivity prediction

the formation of antimicrobial, antifouling and cytotoxic compounds (Almatroudi, 2025; Jayaprakashvel et al., 2020). These metabolites frequently have broad biological action, such as anticancer impacts, by disrupting evolutionarily conserved cellular functions such as DNA replication, protein synthesis, redox balance and membrane integrity. Ecological activity of these compounds can be used to give good understanding on the possible mechanisms of action in cancer cells (Fig. 2).

2.2. Major anticancer-producing marine bacterial genera

Various marine bacterial taxa contain a number of genera that have been consistently identified to be prolific in terms of anticancer metabolites(Bandaru et al., 2025; Dayanidhi et al., 2021). A major most fruitful group of actinomycetes have appeared as marine marine actinomycetes, especially members of the genus Salinispora. The genus Salinispira are obligatory marine bacteria with large genomes that are highly enriched with biosynthetic gene clusters producing polyketides, nonribosomal peptides, and hybrid compounds(Chu et al., 2020; Stonik et al., 2020). The therapeutic potential of Salinispora tropica is illustrated by Salinosporamide A, which is a potent, irreversible proteasome inhibitor and was discovered to have a high potential in oncology research.

The long established genus Streptomyces which is known to contribute to both terrestrial antibiotics and anticancer agents has also marine-adapted species which can produce structurally novel metabolites(Ryu et al., 2021; Stuart et al., 2020). Strains of Streptomyces that were obtained in the marine environment have been found to produce such compounds as thiocoraline, a DNA-intercalating agent, which has good antitumor activity, and a number of macrolides, peptides, and alkaloids that possess cytotoxicity. Such genetic and metabolic diversity of the genus Streptomyces renders it a staple in the marine natural product discovery(Donald et al., 2022; Yang et al., 2020).

Other genera of marine bacteria that are important are Pseudoalteramonas, Bacillus, Vibrio, Micromonospora, and Serinicoccus. Pseudoalteromonas species are also known to produce antiproliferative and pro-apoptotic bioactive pigments, peptides and small molecules. The species of Marine Bacillus produce a variety of lipopeptides and polyketides which have an anticancer, antimicrobial, and immunomodulatory effect(Dan et al., 2021; Xiao et al., 2022). The genus Serinicoccus is not well explored but one that has attracted interest after discovery of Seriniquinone that exhibits selective cytotoxicity against melanoma and other cancerous cell types.

The great variety of these genera speaks of the enormous and relatively untapped biosynthetic potential of marine bacteria(Li, 2023; Mishra et al., 2024). Notably, several strains of marine microorganisms cannot be grown in conventional laboratory methods indicating that the existing findings are just a small proportion of the existing chemical space. Improvements in growing systems, co-culture systems and in situ simulation of marine conditions are slowly opening up this stashed diversity.

2.3. Secondary metabolite biosynthetic pathways

Such a great diversity of marine bacterial metabolites is supported by highly advanced biosynthetic pathways that are encoded in their genomes(Hemmerling and Piel, 2022; Wei et al., 2023). The most notable systems that are involved in the production of complex anticancer compounds are polyketide synthase (PKS) and nonribosomal peptide synthetase (NRPS). These enzymatic systems in modules allow the addition of the variety of building blocks to produce metabolites that are highly structurally complex and functional. Hybrid PKS-NRPS pathways continue to increase chemical diversity as they are a combination of two systems (Hwang et al., 2020; Prado-Alonso et al., 2022).

Besides PKS and NRPS pathways, marine bacteria also utilise a wide range of other biosynthetic pathways, such as terpene biosynthesis, biosynthesis of ribosomally synthesised and post-translationally modified peptides (RiPPs) and shikimate biosynthesis. The unusual functional groups, halogenation and unusual stereochemical structures commonly present in marine bacterial metabolites are commonly thought to be

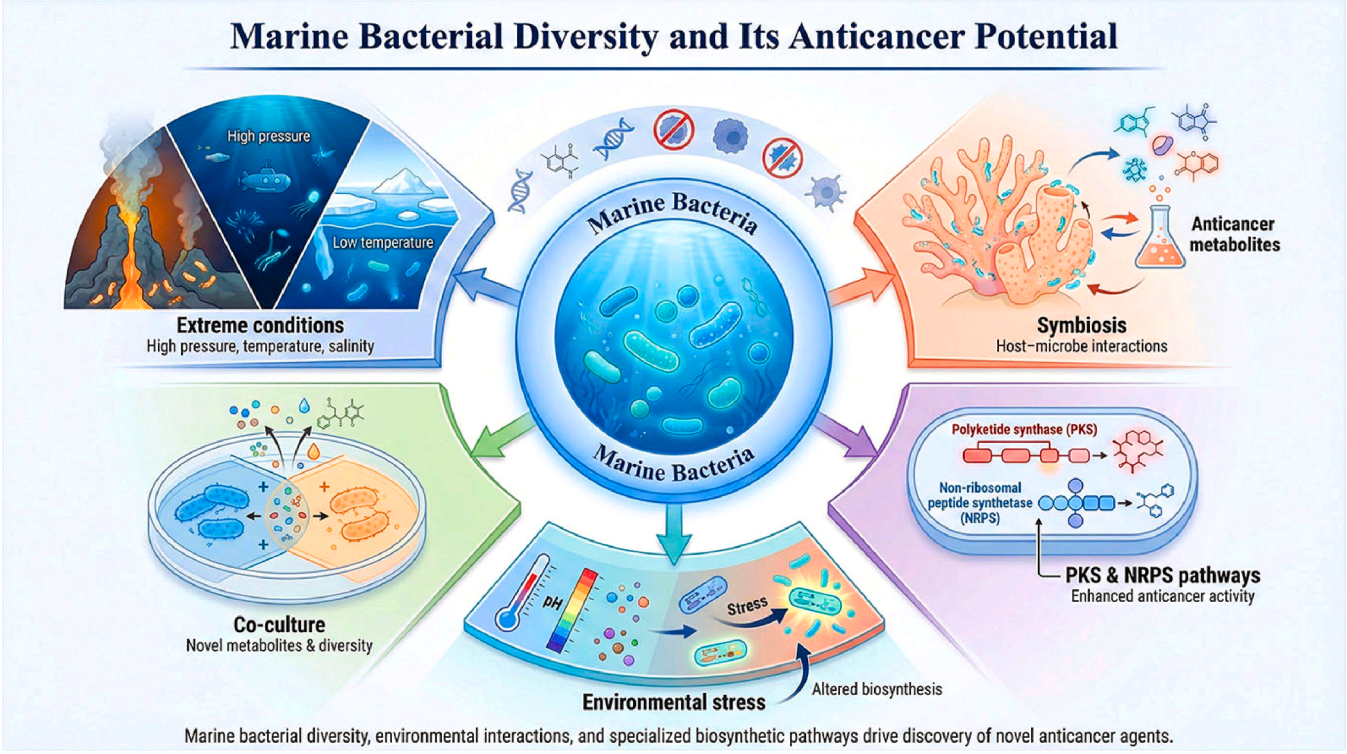

Fig. 2. This diagram illustrates the marine bacterial diversity and its potential in anticancer drug discovery. It highlights extreme environmental conditions, co-culture systems, microbial symbiosis, and specialized biosynthetic pathways, such as PKS and NRPS.

explained by the existence of tailoring enzymes, including halogenases, methyltransferases and oxidoreductases(Crowe et al., 2021; Menon et al., 2022).

The horizontal gene transfer is a essential part of the biosynthetic environment of marine bacteria. The transfer of biosynthetic sets of genes among coexisting microbial communities enhances a fast chemical innovation and adjustment that leads to the development of new bioactive products(Hemmerling and Piel, 2022; Hug et al., 2020). In genome sequencing and bioinformatics, it has been found that a lot of marine bacterial genomes possess silent or cryptic expression biosynthetic clusters of genes which are not expressed in conventional laboratory settings. The opening of these pathways by genetic manipulation, epigenetic alterations or by the environment is a promising approach to the identification of new anticancer agents(Chen et al., 2022; Xu et al., 2023).

Together, these exceptional heterogeneity of marine environments, taxa, and biosynthetic pathways informs their enormous potential as a source of next-generation anticancer compounds. To help direct rational bioprospecting programmes and convert marine-derived natural products into clinically useful cancer therapeutics, a better understanding of marine bacterial diversity and metabolic capabilities is needed (Table 2).

3. Marine bacterial anticancer compounds: chemical classes

Marine bacteria generate an unprecedented diversity of chemically diversified secondary metabolites which have strong anticancer properties(Chen et al., 2020; Kaleem and Saeed, 2024). In contrast to most synthetic chemotherapeutics, they are regularly designed to have the unique molecular scaffolds and multifunctional pharmacophores to allow them to selectively target the cancer-associated pathways. Chemical diversity in marine bacterial metabolites is an indicator of the evolutionary pressures in marine ecosystems, in which space and resource competition has led to the evolution of complex chemical defence mechanisms(Avila, 2021; Deng et al., 2022). The section will classify the marine bacterial anticancer compounds in major chemical classes with examples of the compounds, their structural attributes, and application in cancer treatment.

3.1. Alkaloids and quinones

The most notable example of marine bacterial metabolites that have anticancer properties is represented by alkaloids and quinone-containing molecules(Bhabal and Shimpi, 2025; Hai et al., 2022). These compounds are often very cytotoxic and have redox potential and are able to disrupt important cellular events like DNA replication, mitochondrial activity and protein homeostasis.

An excellent case in point is a quinone-derived metabolite called Seriniquinone that was identified by a marine bacterium named Serinicoccus sp. Seriniquinone has elicited much interest because of its more selective cytotoxicity in melanoma and other cancer cell lines, in comparison to its rather lower toxicity in normal cells. Mechanistic research has found that Seriniquinone acts on cancer-related proteins that mediate cellular stress responses and causes apoptosis in mitochondrial dysfunctional and oxidative stress pathways(Matulja et al., 2020; Talib et al., 2021). Its quinine group allows its redox cycling, resulting in the production of reactive oxygen species (ROS) that is selective in overwhelming the antioxidant defence of cancer cells.

Bacterial alkaloids in the marine environment are usually based on heterocycle containing nitrogen which enables the interaction with the nucleic acids and proteins(Elsaeed et al., 2023; Schneider, 2020). The consequences of these interactions may be DNA intercalation, topoisomerases inhibition or transcriptional regulation. In spite of the fact that the alkaloids of marine bacteria receive less attention than those of terrestrial origin, there is an emerging evidence indicating that these represent an unexploited pool of compounds with great potential as anticancer agents. Quinone-based and alkaloid metabolites are structural novelties that show high biological activity and so promise more pharmacological streamlining(Jadala, 2025; Mumtaz et al., 2025) (Fig. 3).

3.2. Peptides and depsipeptides

Another significant group of anticancer agents occurring in sea bacteria are the peptides and depsipetides(Rafieezadeh and Abbaspour, 2024; Rafieezadeh and Esfandyari, 2024). They are usually produced through nonribosomal peptide synthetase (NRPS) pathways which permit the use of non-proteinogenic amino acids, non-standard functional groups, and cyclic complexes. These characteristics usually give increased stability, particularity and bioactivity**.** Although didemnins were originally isolated in relation to marine tunicates, it is now known that had microbial origins and has been associated with marine bacterial biosynthesis. In particular, Didemnin B demonstrates the potent anticancer effect due to the inhibitive nature of protein synthesis and triggering apoptosis. It disrupts the elongation factor 1a (EF-1a), thus disrupting translational elongation of proliferating cancer cells. In spite of the clinical development of Didemnin B being curtailed due to the toxicity, the structural framework of Didemnin B led to the development of analogues that had better therapeutic indices(Ali et al., 2025; Nie et al., 2024).

A bicyclic depsipeptide, another prominent peptide, is thiocoraline, which is synthesised by marine-bred Streptomyces species. The anticancer action of thiocoraline is mainly associated with DNA bisintercalation, and the DNA replication and transcription are inhibited(Ali et al., 2025; Rafieezadeh and Esfandyari, 2024). The compound has proven to be very cytotoxic to some of the tumour cell lines as well as those that do not respond to other standard chemotherapeutic agents. It is the high specificity of thiocoraline to DNA that makes marine bacterial peptides promising therapeutic agents as targeted anticancer agents.

Antiproliferative and pro-apoptotic activities are also exhibited by

Table 2
This table presents marine bacterial habitats, types, environmental stressors, metabolic adaptations, and examples of anticancer-producing genera. It highlights their role in producing bioactive compounds, especially in cancer therapeutics.

Habitat	Bacteria Type	Environmental Stress	Metabolic Adaptation	Bioactive Compounds	Examples of Anticancer Bacteria
Deep-sea	Piezophilic	High pressure, low temperature	Unusual structural metabolites	Cytotoxic, antiproliferative	Salinispora tropica
Hydrothermal Vents	Thermophilic	High temperature, high metal	Heavy metal-resistant metabolites	Antimicrobial, anticancer	Streptomyces spp.
Hypersaline	Halophilic	High salinity, low nutrients	Osmoprotective metabolites	Cytotoxic, antifouling	Pseudoalteromonas spp.
Symbiotic	Marine Invertebrate	Host-symbiotic interactions	Defensive secondary metabolites	Cytotoxic, anticancer	Serinicoccus spp.
Coastal	Vibrio spp.	High salinity, nutrient-rich	Polyketides, peptides	Cytotoxic, antimicrobial	Bacillus spp.
Marine Sediments	Micromonospora spp.	Low light, high competition	Unique secondary metabolites	Antitumor, immunomodulatory	Streptomyces spp.

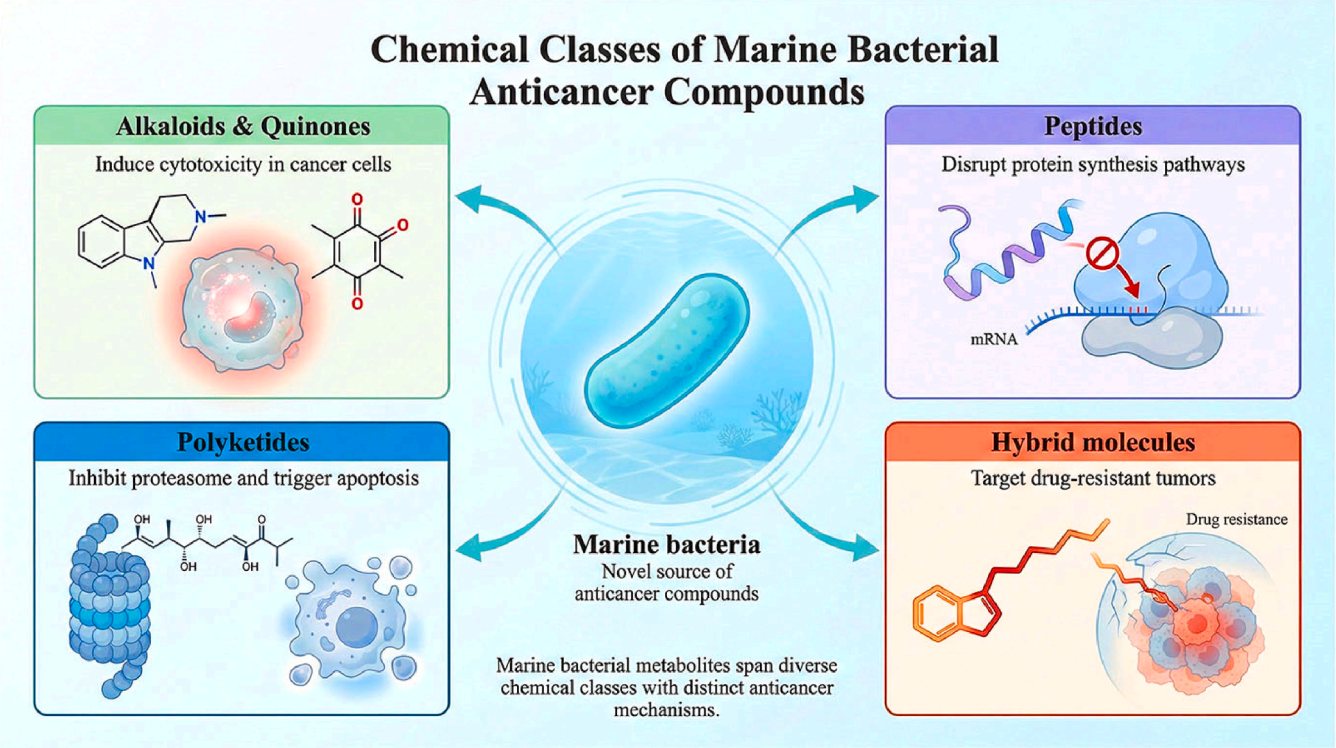

Fig. 3. The figure illustrates the diverse chemical classes of marine bacterial anticancer compounds, including alkaloids, quinones, peptides, polyketides, and hybrid molecules. These compounds target cancer pathways, offering promising solutions for anticancer therapies.

marine bacterial lipopeptides which are generated by genera of Bacillus and Pseudoalteromonas(do Amaral et al., 2023; Martyniuk et al., 2020). These molecules tend to affect membrane integrity, alter signalling pathways or trigger immune responses and are also part of their anticancer activity. The marine peptides and depsipetides have structural diversity with strong biological activities, hence its significance in the study of oncology of the sea.

The ecological diversity of marine bacteria has produced peptides and depsipeptides with highly selective anticancer activities across both hematologic and solid tumors. In leukemia, thiocoraline from Micromonospora marina and BE-22179 exhibit sub-nanomolar cytotoxicity via DNA polymerase inhibition and FOXM1 downregulation, while romidepsin from Chromobacterium violaceum No. 968 induces reactive oxygen species, DNA fragmentation, and G1 phase arrest through histone deacetylase inhibition (Ahmed et al., 2025a). In lymphoma, cyclic depsipeptides such as romidepsin and Piperazimycins A-C, as well as Proximicin B from actinomycetes, promote apoptosis through caspase activation, DNA fragmentation, HDAC inhibition, and ROS generation, whereas amphibian-derived Magainins induce necrotic cell death (Ahmed et al., 2025b). In malignant melanoma, Urukthapelstatin A from Mechercharimyces asporophorigenens and thiocoraline suppress FOXM1, and Lajollamycin, a mixed polyketide-peptide compound from Streptomyces nodosus, decreases melanoma cell viability (Ahmed et al., 2023). For prostate cancer, Chromopeptide A from Chromobacterium sp. HS-13–94 exerts nanomolar cytotoxicity in PC-3, DU145, and LNCaP cells and in vivo xenografts via caspase-3 activation, PARP cleavage, HDAC inhibition, G2/M arrest, and p53 upregulation (Ahmed et al., 2022a). In cervical cancer, lipopeptides such as FW523–3 from Micromonospora chalcea and Iturins A8 and A9 from Bacillus species induce apoptosis and modulate ERK and p38 MAPK pathways while reducing cell viability (Ahmed et al., 2022b). Collectively, these marine bacterial peptides leverage structural diversity derived from ecological adaptation to enact mechanisms ranging from DNA replication inhibition and transcription factor suppression to epigenetic modulation, ROS induction, and cell cycle control, making them highly promising candidates for preclinical development and clinical translation in oncology.

3.3. *Polyketides and macrolides*

Polyketides are among the most structurally diverse and largest classes of marine bacteria anticancer compounds(Lu et al., 2020; Stonik et al., 2020). These metabolites are usually synthesised via polyketide synthase (PKS) pathways, have complex carbon skeletons, contain multiple stereocenters and very diverse functional groups that allow specific interactions with cellular targets.

One of the most technologically advanced marine bacterial polyketides in the clinical development stage is Salinosporamide A which is a derivative of the marine actinomycote Salinispora tropica(Jensen, 2022; Kim et al., 2020). It acts as a very powerful and irreversible proteasome inhibitor, the 20S, which causes the build-up of proteins with misfolds and consequently results in apoptosis on cancer cells. Salinosporamide A has shown a high level of activity in the treatment of haematological malignancy, solid tumours, and those with resistance to other available proteasome inhibitors. The success of it demonstrates the promise of marine bacterial polyketides to provide first-in-class anticancer agents (Jethwa et al., 2023; Rice et al., 2025).

Another very significant group of polyketides is the macrolides, which have large lactone rings. The marine-derived macrolides tend to have cytotoxic, antiangiogenic and immunomodulatory effects (Dolmatova and Dolmatov, 2021; Haque et al., 2022). Even though numerous macrolides were identified in marine invertebrates, there is growing evidence that their biosynthesis is often catalysed by the related marine bacteria. The multiple cellular targets of the macrolide allow them to be considered as useful combinations and multifunctional anticancer agents.

The polyketide and macrolide structural complexity is not only difficult to synthesise in a chemical manner but also offers ways in which the structure-activity relationship can be studied and rational drug design can be carried out(Carretero Molina, 2024; Myers and Clark, 2021). The development of synthetic biology and biosynthetic

engineering is beginning to allow the production and customization of these compounds in large quantities and therefore they are on the path to clinical use.

3.4. Hybrid and structurally novel molecules

Hybrid molecules that are synthesised via concerted PKS-NRPS signalling are an exceptionally promising sub-group of marine bacterial anticancer molecules(Carretero Molina, 2024). These metabolites combine characteristics of polyketides and nonribosomal peptides and produce very complex structures with increased functional diversity. These hybrid compounds tend to exhibit more than one mechanism of action which makes them more effective against heterogeneous and drug-resistant tumours.

The marine bacteria also synthesise various structurally novel molecules that cannot be classified in a mainstream way. These consist of halogenated compounds, atypical cyclic structures and metabolites with rare functional groups that are hardly found in natural products on the earth(Zhang et al., 2025). Halogenation is a common feature in marine bacterial metabolites, and may have a very high impact on biological activity, through increasing membrane permeability, metabolic stability, and affinity of target binding.

These new structures have been made available by the significant improvements in analytical capabilities including high-resolution mass spectrometry, nuclear magnetic resonance spectroscopy and dereplication by metabolomics(Letertre et al., 2020; Letertre et al., 2021). These technologies together with genome mining techniques are discovering a growing repertoire of hitherto unknown marine bacterial metabolites with anticancer properties.

3.5. Structure–activity relationships and chemical optimization

It is important to comprehend the correlation between chemical structure and biological activity in order to develop marine bacterial anticancer compounds successfully. Narrow therapeutic windows of many marine-derived molecules or unfavourable pharmacokinetics of transduction of marine-derived molecules require chemical optimization(Letertre et al., 2020; Letertre et al., 2021). The structure-activity relationship (SAR) research has given useful clues in regards to the functional groups and structural motifs that play a role in anticancer activity thereby guiding the development of analogues with a better potency, selectivity, and safety.

The drug-like properties of marine bacteria metabolites have been increased by using semi-synthetic modification and total synthesis strategies(Goel et al., 2024; Narayanan and Rajinikanth, 2025). Moreover, biosynthetic engineering makes it possible to produce novel analogues through alteration of enzymatic pathways providing a strong alternative to classical chemistry synthesis. All these measures lead to increased translational potential of marine bacterial anticancer compounds.

To conclude, marine bacteria synthesise a broad range of anticancer molecules including alkaloids, quinones, peptides, polyketides, macrolides, and hybrid molecules(Mbaoji et al., 2021; Santos et al., 2020). These metabolites are of great value as a source of next-generation anticancer therapeutics due to the extraordinary chemical diversity and unusual mechanisms of action. Further discovery and streamlining of these classes of chemicals is essential in converting marine bacterial natural products into clinically useful cancer therapeutics (Table 3).

4. Molecular mechanisms of anticancer action

Marine bacterial anticancer compounds have their therapeutic action due to a broad spectrum of molecular pathways that act on cancer hallmarks, such as uncontrolled proliferation, resistance to cell death, metabolic reprogramming, and immune evasion(Bandaru et al., 2025; Dayanidhi et al., 2021). In comparison to most traditional chemotherapeutic drugs, which do act by rather specific pathways, marine bacterium metabolites are frequently multi-targeted, which allows them to alter multiple oncogenic pathways all at the same time. It is this multifunctionality that is especially beneficial when dealing with tumour heterogeneity and resistance to drugs. The subsequent subsections provide an explanation of the major molecular pathways through which marine bacterial metabolites have anticancer effects(Esposito et al., 2022; Riera-Romo et al., 2020).

4.1. Induction of apoptosis and cell cycle arrest

The sea marine bacterial metabolites induction of programmed cell death (apoptosis) is one of the most well-documented anticancer mechanisms. Apoptosis is an essential homostatic process in tissues and the malfunction of this process is one of the indicatures of cancer development and resistance to drugs(Chaudhry et al., 2022a; Morana et al., 2022). Most marine bacterial products trigger intrinsic (mitochondrial) and/or extrinsic apoptotic pathways and cause cancer cell selective ablation.

Metabolites produced in the sea like Seriniquinone, thiocoraline have been reported to destabilise membrane potential in the mitochondrion, and lead to cytochrome c leakage and caspase cascades (Mirra and Marfany, 2024; Silva et al., 2023). The end result of this process is the breakdown of DNA and death of apoptotic cells. These compounds have been shown to regulate the expression of pro and anti-apoptotic proteins, such as Bcl-2 family members, in a number of cancer cell models and to shift the apoptosis-survival balance. Significantly, the increased sensitivity of the cancer cells to mitochondrial stress is commonly observed because of the corresponding change in the metabolic state, which can be one of the factors in the selective cytotoxicity of the particular marine bacterial compounds(Aloufi et al., 2023; Riera-Romo et al., 2020).

Marine bacterial metabolites often cause cell cycle arrest at critical checkpoints in addition to apoptosis, e.g. the G1/S or G2/M transitions (Fares Amer and Luzzatto Knaan, 2022; Sun et al., 2021). These compounds block DNA replication and mitotic advancement in quickly dividing tumour cells by blocking or lowering cyclin-dependent kinases (CDKs) or the cyclins. Metabolites based on polyketides such as Salinosporamide A have been shown to cause arrest of the cell cycle by disrupting proteostasis and misfolded protein accumulation to activate the checkpoint. Cell cycle arrest can suppress the proliferation of tumour cells in addition it can sensitise cancer cells to apoptosis as well as increase the effectiveness of combination therapies(Matthews et al., 2022; Salam et al., 2021) (Fig. 4).

Table 3
This table summarizes various chemical classes of marine bacterial anticancer compounds, highlighting examples, molecular scaffolds, and mechanisms of action, targeted pathways, and key applications in cancer therapy.

Chemical Class	**Examples**	Molecular Scaffold	**Mechanism**	Targeted Pathways	Key Application
Alkaloids	Seriniquinone	Quinone	Redox cycling, ROS production	Mitochondrial dysfunction	Selective cytotoxicity
Quinones	Seriniquinone	Quinone	Redox cycling, ROS production	Cancer cell apoptosis	Melanoma treatment
Peptides	Didemnin B	Cyclic peptide	Protein synthesis inhibition	Apoptosis	Protein synthesis disruption
Depsipeptides	Thiocoraline	Bicyclic depsipeptide	DNA bisintercalation	Transcription inhibition	Targeted anticancer agent
Polyketides	Salinosporamide A	Complex carbon skeletons	Proteasome inhibition	Tumor apoptosis	Hematological malignancy
Hybrid Molecules	Halogenated compounds	Hybrid PKS-NRPS	Multiple mechanisms	Heterogeneous tumor targeting	Drug-resistant tumors

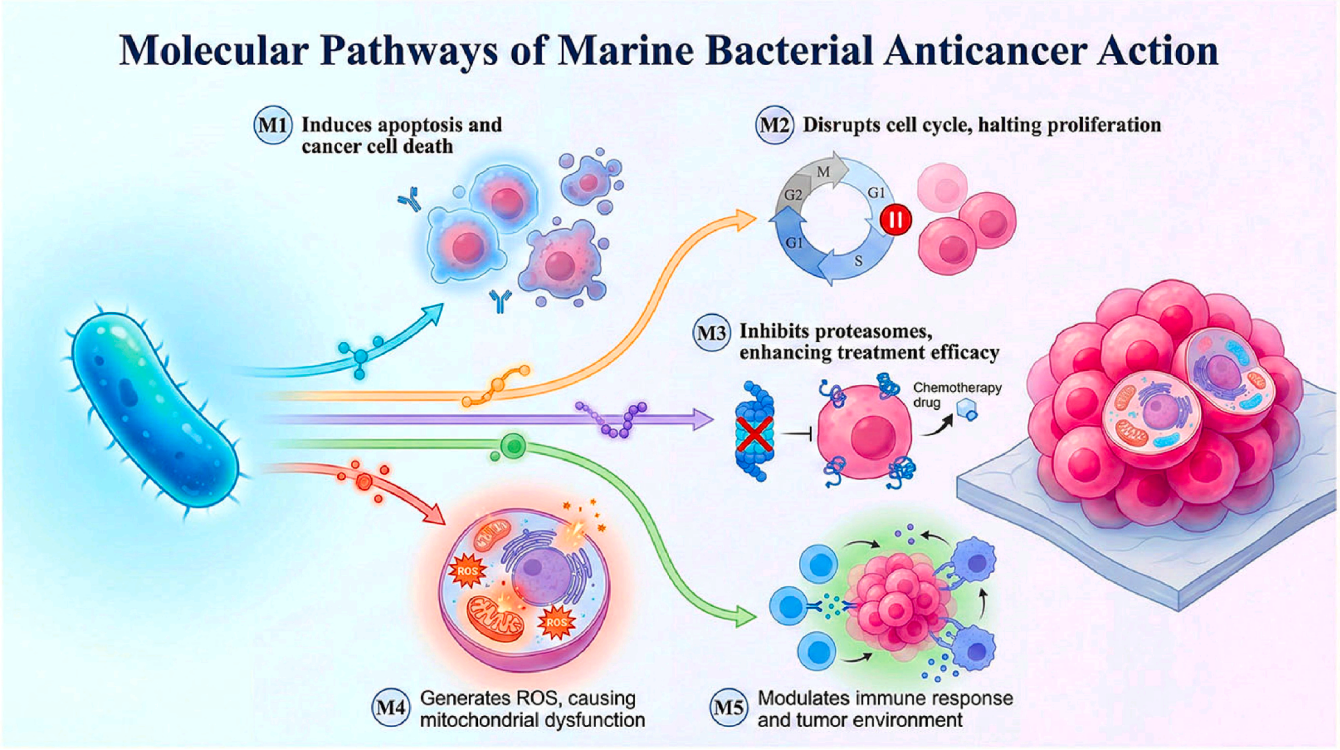

Fig. 4. This figure illustrates the molecular pathways through which marine bacterial metabolites exhibit anticancer activity. The mechanisms include inducing apoptosis, disrupting the cell cycle, inhibiting proteasomes, generating ROS, and modulating immune responses.

4.2. Proteasome and ubiquitin-proteasome pathway inhibition

UPS The ubiquitin-proteasome system (UPS) plays an important role in protein turnover, cell cycle, and signal transduction(Li et al., 2022; Park et al., 2020). The proteasome is critical to cancer cells in ensuring that they deal with higher protein synthesis and preserve oncogenic signalling. UPS targeting has hence become an efficient anticancer method especially in hematologic tumours.

Bacterial metabolites in the ocean have also been useful in this therapeutic paradigm with Salinosporamide A being a historic one (McCauley et al., 2020; Stennett et al., 2020). This compound is known to inhibit the chymotrypsin-like action of 20S proteasome reversibly by modifying the active site of the proteasome covalently. Inhibition of proteasomes causes the ubiquitination and misfolding of proteins, which causes endoplasmic reticulum stress, unfolded protein response, and apoptotic cell death. Marine-derived proteasome inhibitors usually have increased potency and resistance-overcoming properties as compared to first-generation proteasome inhibitors.

In addition to direct proteasome inhibitor, the UPS of other marine bacteria is regulated by other components upstream of proteasomes such as E3 ubiquitin ligases and de-ubiquitinating enzymes. Through changes in protein stability and degradation, these metabolites have the ability to indirectly suppress oncogenic signaling including NF-kB, p53 and MYC signaling(Chan et al., 2024; Trejo-Solís et al., 2024). Targeting proteostasis is the capacity to adjust proteostasis, a potent approach through which marine bacteria metabolites score anticancer action.

4.3. Oxidative stress and mitochondrial dysfunction

Cancer cells are generally characterised by high levels of the reactive oxygen species (ROS) because of metabolic and oncogenic destabilisation(ArulJothi et al., 2022; Kirtonia et al., 2020). Whereas a moderate concentration of ROS may stimulate tumour growth and survival, the extreme concentration of oxidative pressure may overwhelm antioxidant-mediated defence mechanisms and result in cell death. Lots of marine bacteria anticancer substances take advantage of this susceptibility and further elevate the level of intracellular ROS or disable antioxidant mechanisms.

The quinone based metabolites including Seriniquinone, have a special application in redox regulation(Ansari and Dar, 2025; Mumtaz et al., 2025). These compounds cause redox cycling leading to the production of ROS that destroy cellular macromolecules, such as DNA, lipids, and proteins. The oxidative stress, which results, produces mitochondrial dysfunction, membrane potential loss, and intrinsic apoptotic pathway activation(Jurcau, 2021; Kowalczyk et al., 2021). It is worth noting that normal cells that usually have stronger antioxidant capability and lower basal levels of ROS tend to be less subject to such a mechanism, which leads to the therapeutic selectivity of marine-derived compounds.

The mitochondrial targeting is not limited to the production of ROS. Certain bacterial metabolites in the marine directly inhibit mitochondrial respiration, ATP generation, or mitochondrial dynamics(Fadda et al., 2025; Khan et al., 2020). These compounds disrupt the process of energy metabolism and interfere with the processes of the cancer cells that are selectively disabled by the compounds due to the existence of other non-targeted metabolic pathways that encourage the rapid proliferation of the cancer cells. Mitochondrial dysfunction is also overlapping with other cell death pathways such as apoptosis and necroptosis and enhances the anti-cancer effects of the agents.

4.4. Autophagy modulation and cancer cell fate

Autophagy is a cellular process that is conserved and plays the role of degrading and recycling damaged organelles and macromolecules(Li et al., 2021; Yun et al., 2020). Autophagy has two functions in cancer: it may help tumour cells to survive stress, yet an overabundance or malcontrolled autophagy might result in autophagic cell death. Marine bacterial anticancer compounds were demonstrated to have context-dependent autophagy modulation.

Certain marine metabolites cause autophagy as a pro-death pathway,

which occurs especially in cancer cells that are resistant to apoptosis (Bachar et al., 2022; Rahman et al., 2021). These compounds stimulate cell death and autophagic flux to a level that would guarantee survival. Other marine bacterial metabolites, on the contrary, suppress protective autophagy, therefore, predisposing the cancer cells to apoptosis and the effectiveness of chemotherapeutic agents. The manipulation of autophagy potential which is shown by this ability demonstrates the versatile nature of marine bacterial compounds in its therapy and its possible applicability in combination therapeutics(Dyshlovoy, 2020; Eze et al., 2023).

4.5. Immune modulation and tumour microenvironment targeting

There is also emerging evidence that marine bacterial anticancer metabolites have the capacity to regulate immune responses and also have an effect on the tumour microenvironment, which has played a growing role as a target in contemporary oncology. Some of the compounds of marine origin have been found to increase antitumor immunity by inducing immunogenic death in cells, which involves cell release of danger-associated molecular patterns to trigger immune response to tumour cells(Liu et al., 2024; Qu et al., 2024).

Besides, marine bacterial products have been found to inhibit protumorigenic inflammation, angiogenesis and alter immune checkpoint pathways. These compounds provide a comprehensive treatment of cancer since they can not only attack the cancer cells, but the microenvironment also. The immunomodulatory properties also provide a possibility to utilise marine-derived compounds together with immunotherapies, which may increase the response rates and levels(Gamberi et al., 2024; Sanapala et al., 2022).

4.6. Multitarget actions and overcoming drug resistance

The resistance to the drugs is a significant barrier in the treatment of cancer and may occur as a result of genetic mutations, overexpression of efflux pumps, altered drug targets or compensatory signalling pathways (Bou Antoun and Chioni, 2023; Lee et al., 2020). This is due to the circumvention of standard resistance mechanisms by the multitargeting capability of many marine bacterial anticancer compounds. The compounds can suppress the emergence of resistance because they interrupt various cellular functions at once, including the process of proteostasis, redox equilibrium, and signal transduction.

In addition to this, certain marine bacterial metabolites have been proven to be effective in fighting cancer cells resistant to conventional chemotherapeutics which highlights the fact that they can serve as a second-line or combination therapy. They have different mechanisms of action, which are not the same as the conventional drugs, and are useful in the struggle against refractory and relapsed cancer(Marine et al., 2020; Marzagalli et al., 2021).

Overall, the marine bacterial anticancer compounds have a wide range of molecular pathways that they act as shown by induction of apoptosis, inhibition of proteasome, regulation of oxidative stress, control of autophagy, stimulation of immune response and circumvention of resistance. Such mechanistic diversity can not only be the foundation of their potent anticancer efficacy but also can make marine bacteria a valuable source of new therapeutic approaches that will be able to meet the multifaceted challenges of the modern oncology (Table 4).

5. Preclinical and translational evidence

In-vitro and in-vivo studies have proved significant anticancer effects on a wide spectrum of cancerous malignancies including haematological malignancies, as well as non-metastatic such as solid tumours that are not curable with traditional agents (Anvar et al., 2024; Yan et al., 2025). The research works offer important evidence of efficacy, selectivity, pharmacodynamics, and safety, thus establishing the basis of clinical translation (Fig. 5).

5.1. In-vitro anticancer studies

In-vitro screening continues to be an important pillar of anticancer drug discovery and marine bacterial metabolites have continued to demonstrate excellent cytotoxic and antiprolliferative effects in almost all cancer cell models. Salinosporamide A, Seriniquinone, thiocoraline and other lipopeptides which are of marine origin have been tested against human cancer cell lines consisting of breast, lung, colon, prostate, melanoma, leukaemia, and multiple myeloma cells(Bahrami et al., 2022; Srinivasan et al., 2020). Low micromolar to nanomolar levels of inhibition are often reported in these studies and indicate the high level of potency of marine bacterial metabolites.

Notably, there are a number of marine-derived compounds which have selectivity on cancer cell as opposed to non-transformed cells or normal cells(Catanzaro et al., 2020; Pereira, 2023). This specificity has been explained by the fact that the cancer vulnerabilities targeted tend to be cancer specific proteasome dependency, oxidative stress, or cell cycle control. As an example, Seriniquinone has been shown to have selective cytotoxicity on melanoma cells which is associated with their selective expression of molecular targets and increased sensitivity to oxidative stress in cancer cells. Equally, marine bacterial proteasome inhibitors demonstrate a greater action in cancerous cells of high protein turnover and metabolic strain.

Mechanistic in-vitro studies also support the description of the molecular pathways in the previous sections such as the induction of apoptosis and arrest cell cycle plus disruption of proteostasis (Abbas and Larisch, 2021; Frolova et al., 2023). The studies often use the flow cytometry, gene expression and proteomic profiling to explain the downstream action of the marine bacterial metabolites. Taken together, in-vitro evidence suggests solid reasons which besides their strong anticancer properties and mechanistic specificity, marine bacterial compounds should be advanced to in-vivo testing.

Table 4
The table summarizes the major molecular mechanisms through which marine bacterial metabolites exhibit anticancer effects, focusing on their impact on apoptosis, cell cycle, oxidative stress, proteasome inhibition, autophagy modulation, and immune responses. These compounds operate via multi-targeted approaches that can overcome drug resistance and improve cancer therapy.

Mechanism	Marine Compound(s)	Target Pathway	Effect on Cancer Cells	Mechanism Type	Therapeutic Application
Induction of Apoptosis	Seriniquinone, Thiocoraline	Apoptotic Pathways	DNA Breakdown, Cell Death	Direct Action	Apoptosis Induction
Cell Cycle Arrest	Salinosporamide A	G1/S, G2/M Transitions	Blocked DNA Replication	Cell Cycle Control	Tumor Proliferation Control
Proteasome Inhibition	Salinosporamide A	Proteasome Pathway	Protein Misfolding, Stress	Indirect Action	Resistance Overcoming
Oxidative Stress	Seriniquinone	ROS Production	Mitochondrial Dysfunction	Redox Cycling	Targeted Cytotoxicity
Autophagy Modulation	Marine Metabolites	Autophagic Pathways	Controlled Cell Death	Context-Dependent	Chemotherapy Sensitization
Immune Modulation	Marine Metabolites	Tumor Microenvironment	Immune Response Enhancement	Immunomodulation	Combination Therapy Potential

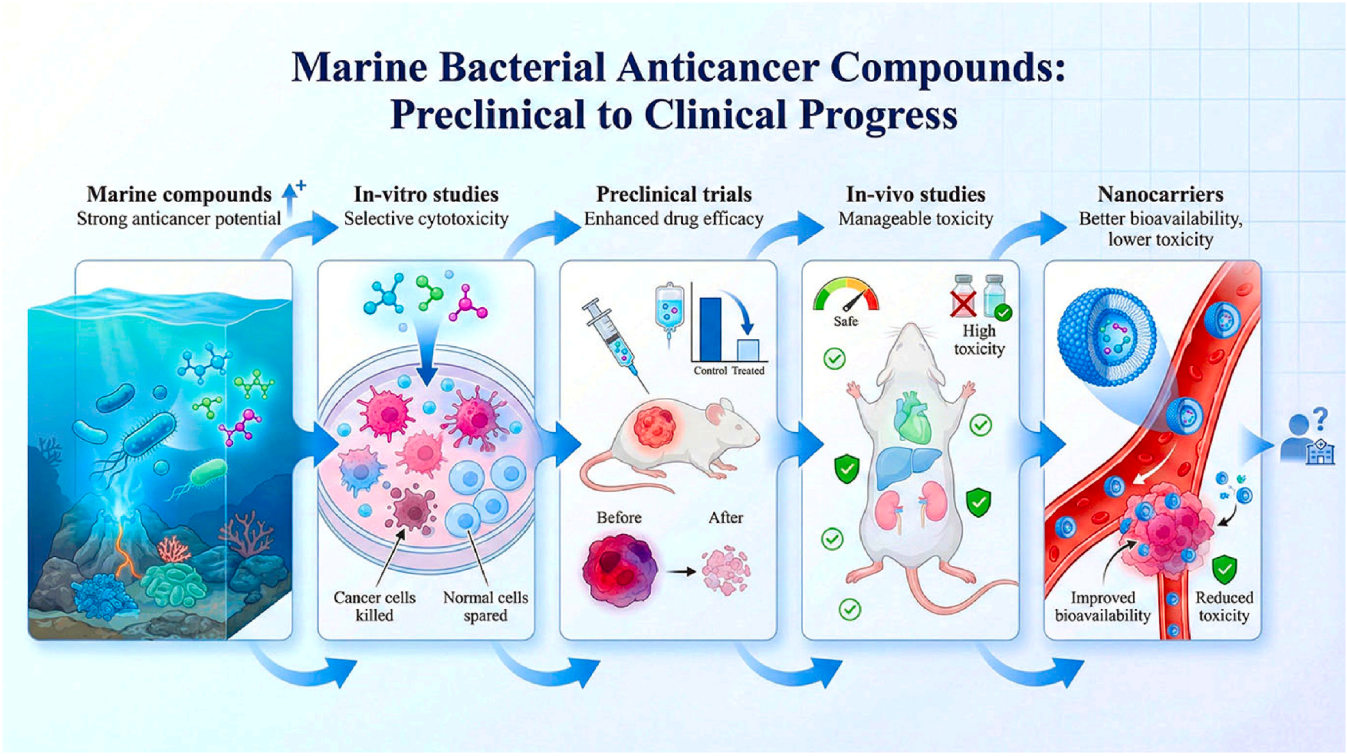

Fig. 5. This figure illustrates the progression of marine bacterial anticancer compounds from preclinical studies to clinical applications, highlighting their anticancer potential, selective cytotoxicity, drug efficacy, manageable toxicity, and the role of nanocarriers.

5.2. Efficacy and toxicity studies in-vivo

The in-vivo experiments are required to determine the therapeutic significance of marine bacterial anti-cancer compounds, which offer the data on the pharmacokinetics, bioavailability, toxicity, and antitumor properties on the physiologically relevant systems. Animal models that have been extensively utilised to test marine-derived compounds are animal xenograft and syngeneic tumour models(Wang et al., 2020; Zuo and Kwok, 2021).

Salinosporamide A is one of the most well-investigated marine bacterial metabolites that are studied in in-vivo conditions. Preclinical trials have shown that this compound can inhibit tumour growth and extend life of the mouse with multiple myeloma, lymphoma and solid tumours. Notably, the Salinosporamide A has demonstrated activity on tumours that have become resistant to the first-generation proteasome inhibitors, which suggests that the drug will be able to overcome resistance developed over time. Toxicity tests have shown that it has a manageable safety profile at therapeutically effective doses and it should be developed further to clinical trials.

Several other bacterial metabolites in the marine environment have been promising in-vivo(Barzkar et al., 2024; Modolon et al., 2020). The effect of thiocoraline on tumour growth suppression was proven in xenograft models even though development of thiocoraline has been limited due to dose-limiting toxicity, making it important to optimise and develop analogues carefully. Marine Bacillus and Streptomyces species have been shown to cause antitumor activity in animal models by the action of inducing apoptosis, immune modulation and angiogenesis inhibition(Chaudhry et al., 2022b; Nathan and Kannan, 2020).

In-vivo assessment of toxicity is an important factor in assessment. Although there are compounds of some marine bacteria with narrow therapeutic indices, to improve tumor targeting and minimise systemic toxicity, relationship improvements are being considered in terms of nanoparticle delivery system and prodrug approaches. These have been found to promise in terms of enhancing in-vivo efficacies of marine-derived anticancer agents.

5.3. Pharmacokinetics and drug delivery inclusion

One of the biggest problems that confront translation of marine bacterial metabolites into clinical therapeutics is the pharmacokinetic nature of these languages(Albukhari, 2025; Heinrich et al., 2020). Most of the compounds that were derived in the sea have complex structures, high molecular weights, or low solubility that may influence absorption, distribution, metabolism, and excretion. Preclinical pharmacokinetics research has thus been aimed at the maximisation of therapeutic effects by maximising formulation and delivery.

The stability and bioavailability of some marine bacterial metabolites have been found to be enhanced by encapsulation in liposomes, polymeric nanoparticles or other nanocarriers. The advanced delivery systems have the capability to increase tumour accumulation through increased permeability and retention effect, minimise off-target toxicity, and control release of the active compound(Kang et al., 2023; Reddy and Reddy, 2025). Chemical modification and semi-synthetic derivatization have also been used to enhance metabolic stability and oral bioavailability, which also enhance further clinical translation.

5.4. Marine bacterial compounds clinical development

Despite the fact that the list of marine bacterial anticancer compounds that have made it to clinical trials is low, there is a number of good examples that demonstrate the translational potential of this group of agents. A milestone in the development of marine bacterial drugs has been the development of Salinosporamide A that is currently in early-stage clinical trials as a treatment of multiple myeloma and other malignancies(Claridge, 2024; Thissera et al., 2022). It has been shown to be a strong proteasome inhibitor with clinical studies offering useful information regarding the dose, safety and response to therapy.

The other marine-derived compounds such as didemnin analogues and peptide-based ones have also undergone clinical testing, although with mixed results(Dincturk et al., 2025; Shahidi and Saeid, 2025). The challenges of the translation of potent natural products to safe and

effective drugs were evident because some programmes have been discontinued because they were toxic or had low efficacy. However, experience gained during these trials has guided future drug design and optimization efforts such as the need to be selective, deliver and patient stratification.

5.5. Translational problems and prospects

The process of bringing to the clinical setting the results of preclinical success is still complicated and multidimensional. The main issues are how to ensure the availability of compounds sustainably, pharmacokinetic limitations, toxicity and regulatory requirements(Gwanya et al., 2024; Schileo and Grancini, 2021). Nevertheless, as of late, with genome mining, synthetic biology and metabolic engineering, there are more opportunities than ever to overcome these challenges. These technologies are reducing the time-to-clinic timeline of promising compounds on the basis of marine bacterial metabolites through the ability to produce them at scale and rationalize their modification.

Besides, the incorporation of marine bacteria anticancer agents into combination therapies is a promising translational approach. The preclinical experimentation has revealed the synergistic behaviour of marine-derived compounds with the traditional chemotherapeutics, targeted therapies, or immunotherapies(Hemmati and Rasekhi Kazerooni, 2022; Kowalczyk et al., 2025). The combinations can increase efficacy and decrease resistance, as well as reduce the dose and thus, patient outcomes can be improved.

In brief, there is a considerable amount of preclinical and emerging translational data in favour of the anticancer activity of marine bacterial metabolites. Strong in-vitro and in-vivo clinical evidence supports the efficacy, mechanistic specificity and potential resistance circumvention of this therapeutic class and early clinical experience highlights the potential and difficulties of this new class of agents. Current and future research efforts on translational research, new methods of delivery, and interdisciplinary working together will be critical towards achieving the full clinical potential of marine bacterial anticancer compounds (Table 5).

6. Difficulties in marine bacterial development of anti-cancer drugs

Even though marine bacterial anticancer compounds have shown a substantial potential, their successful conversion to clinically-approved therapeutic agents is seen to have numerous scientific, technical, and regulatory difficulties(Bandaru et al., 2025; Wang et al., 2020). Although recent developments in marine microbiology and chemical biology have increased the availability of new bioactive molecules, there are still a number of barriers that reduce the effectiveness and success of marine bacterial drug development. The challenges have to be overcome in order to realize the entire therapeutic potential of marine bacteria in oncology (Fig. 6).

6.1. Sustainability in supply and scalability

A stable and sustainable supply of bioactive compounds is one of the most significant issues that have been in marine life in terms of developing anticancer drugs. Most of the metabolites seen in marine bacteria are produced in very low concentrations either under natural or laboratory conditions, which means that it is not viable to isolate them in large amounts(Hosseini et al., 2022; Stincone and Brandelli, 2020). Also, the marine ecosystems native to the isolated bacteria can be ecologically sensitive or inaccessible, which is of concern to the conservation of biodiversity and sustainability.

Growth of marine microorganisms in itself poses some challenges because, most of them are slow growing or are very specific in their environmental conditions and are challenging to cultivate in the laboratory or industrial environments(Gonzalez and Aranda, 2023; Zhang et al., 2021). More significantly, production of metabolites is frequently affected by minor ecological elements, including nutrient supply, salinity and interactions with other microbes, and result in changes in yield. These problems make it hard to transfer to the industrial level of production needed to develop a clinical discovery to a small-scale discovery.

6.2. Structural complexity and chemical synthesis

The most common characteristics of marine bacterial anticancer compounds are complex and densely functionalized molecular structures, which contain several stereocenters, macrocyclic rings, and unusual functional groups. Although the complexity of such structures is the basis of their powerful biological action, it also poses a serious difficulty in terms of chemical production and optimization(Hirschi et al., 2022; Miserez et al., 2023). The time, cost and technical complexity of the process of total synthesising these molecules is in many cases time consuming, expensive, and technically challenging, which puts constraints on the applicability to generate enough molecules to perform preclinical and clinical research.

Pharmacological properties can be enhanced by semi-synthetic modification of marine bacterial metabolites but this method is limited by the parent compound(Florencia and Brunella, 2024; Said et al., 2025). Also, rational design of drugs and structure-activity relationship research, and lead optimization may be hampered by structural complexity. These difficulties need novel synthetic approaches, and biosynthetic engineering approaches that can allow the production of simplified or optimised analogues without loss of biological function.

6.3. Pharmacokinetics, bioavailability and toxicity

The other significant challenge affecting the development of marine bacterial anticancer agents is unfavourable pharmacokinetic profiles. Compounds derived marine have poor solubility, limited stability or rapid metabolic clearance which may decrease bioavailability and therapeutic efficacy(Shikov et al., 2020; Yang et al., 2020). Such concerns are especially severe when it comes to compounds that are supposed to be administered systemically, where relative and predictable exposure to drugs is essential.

A major concern that exists is toxicity. Although marine bacteria metabolites tend to exhibit selectivity on cancer cells in vitro, off-target and dose-limiting toxicity may appear in vivo. Initial clinical trials on certain compounds of marine origin have highlighted why the toxicity of these compounds should be well examined and the dose should be

Table 5
Summarizes the preclinical evidence supporting marine bacterial metabolites' anticancer activity. It details in-vitro and in-vivo findings, mechanisms of action, and the potential for clinical translation, highlighting challenges and prospects.

Study Type	Marine Compound	Cancer Type	**Mechanism**	In-Vivo Findings	Clinical Translation
In-vitro	Salinosporamide A	Multiple cancers	Apoptosis, Proteasome inhibition	Effective in cell lines	Preclinical support
In-vitro	Seriniquinone	Melanoma	Oxidative stress	Selective cytotoxicity	Pending clinical trials
In-vitro	Thiocoraline	Leukemia, Lymphoma	Apoptosis	Inhibited tumor growth	Toxicity limits development
In-vivo	Salinosporamide A	Multiple Myeloma	Proteasome inhibition	Tumor growth inhibition	Preclinical success
In-vivo	Thiocoraline	Various tumors	Apoptosis, Immune modulation	Tumor suppression	Requires dose optimization
Translational	Marine Bacterial Metabolites	Various cancers	Combination therapy	Enhanced efficacy	Ongoing research

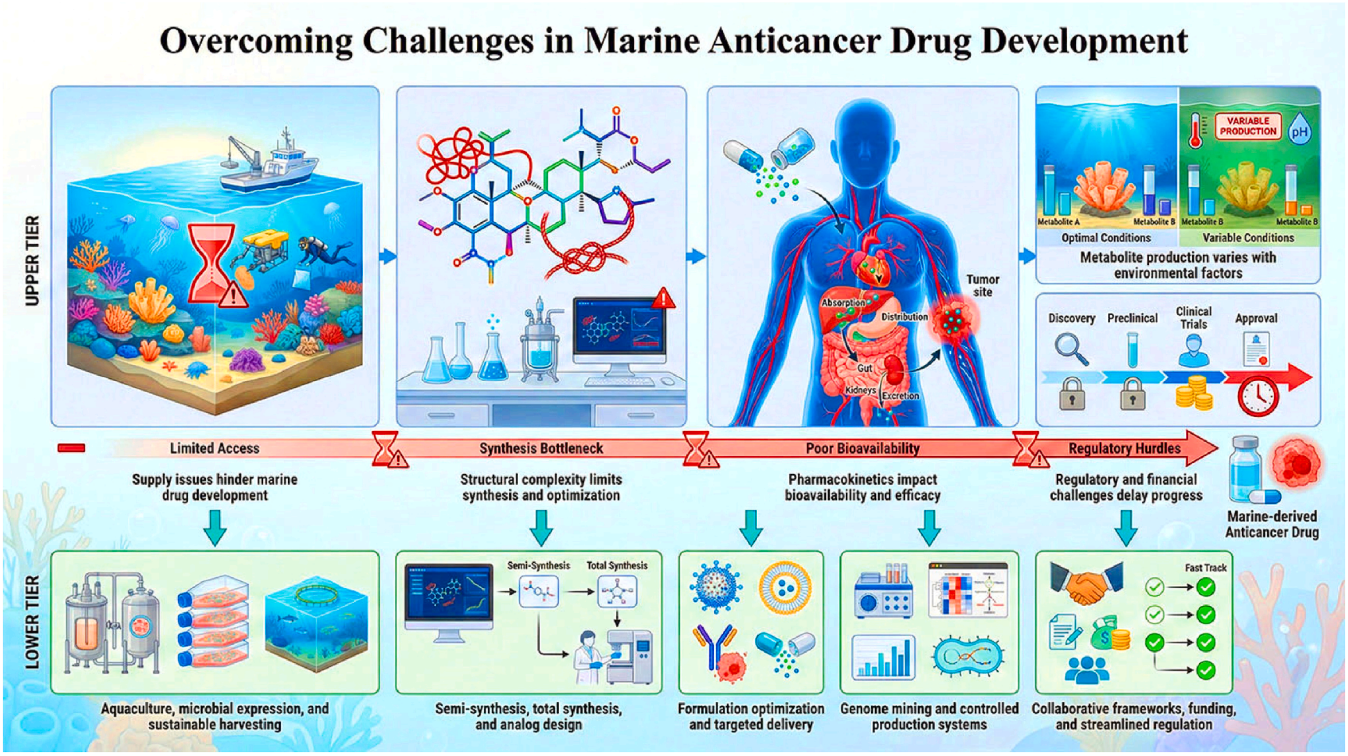

Fig. 6. This figure illustrates the challenges in marine anticancer drug development, highlighting issues such as limited access, synthesis bottlenecks, poor bioavailability, and regulatory hurdles, alongside strategies like semi-synthesis and collaborative frameworks.

optimized. Some of the strategies being considered to reduce the toxicity and enhance therapeutic indices include targeted drug delivery, prodrug design and combination therapy.

6.4. *Metabolite production variability*

The production of secondary metabolites by marine bacteria is often controlled by complicated genetic and environmental influences. Most of the biosynthetic gene clusters have been silent or lowly expressing in normal lab conditions leading to erratic or insignificant synthesis of the desired product(Scherlach and Hertweck, 2021; Wang and Mao, 2025). Such variability makes discovery efforts as well as downstream development more difficult.

Genome mining has shown that there are a huge repertoire of cryptic biosynthetic pathways, however, there is a major challenge in activating these pathways. Co-culture systems, epigenetic modulation and genetic engineering are some of the approaches used to optimise the production of metabolites but these methods still need to be refined and standardised to use them in an industrial scale.

6.5. *Regulatory and environmental issues*

The design of marine based bacterial anticancer drugs are also prone to regulatory and environmental factors which tend to be more complicated than natural products found on the ground. International agreements and national regulations that are used to protect the marine biodiversity and share benefits fairly govern marine bioprospecting (Flemsæter, 2020; Leary, 2020). Managing these regulatory frameworks might be a time-consuming activity that restricts access to some marine resources.

Moreover, before new anticancer drugs are approved, regulatory agencies need detailed information on safety, efficacy and manufacturing procedures. The natural complexity and novelty of marine bacterial metabolites may make the regulatory assessment complex and require strong and well-detailed development pipelines.

6.6. *Translational and economic intelligences*

Lastly, economic variables also are relevant in the development of marine antiprolliferative agents against cancer. The pharmaceutical industry might be discouraged to invest due to high cost of discovery and development, and commercial returns may be uncertain(Hunt and Kirsch, 2020; Leary, 2020). These concerns are worsened by the long times that it takes to develop natural products drugs.

In order to overcome these obstacles, collaborative models with academia on the one hand, industry on the other hand and the public financing agencies are now more and more becoming the rule. The development of synthetic biology, artificial intelligence and high-throughput screening provide possibilities to save the costs and shorten the development schedule. A lot of the problems encountered in the development of marine bacterial anticancer drugs can be gradually solved by incorporating further technological innovation into the development process as well as fostering favourable regulatory and funding frameworks.

To sum it up, marine bacterial anticancer compounds have several enormous therapeutic potential, but their successful conversion into clinically viable drugs demands to overcome very serious obstacles associated with supply, synthesis, pharmacokinetics, toxicity, regulation, and economics. These challenges can be overcome by an interdisciplinary team effort and technological advancement in order to fully harness the potential of the marine bacteria in the treatment of cancer.

7. Future directions

The interplay of the high-tech biotechnology, computation, and precision oncology is the future of marine bacterial anticancer drug discovery. The fastest advancements in genome mining and metagenomic sequencing will result in a huge repertoire of cryptic biosynthetic gene clusters that have not been explored in marine bacteria. The combination of these strategies with synthetic biology and metabolic engineering will allow activating, optimizing, and scaling the

production of novel anticancer metabolites and eliminate the long-standing supply constraint. Tools of artificial intelligence and machine learning are being more and more applied to the natural product research to forecast bioactivity, optimise lead compounds, and simplify the structure-activity relationship analyses to simplify the drug discovery pipeline.

Therapeutically, marine bacterial metabolites have a high potential of being significant in combination and personalised cancer treatment. Most importantly, they are promising as an addition to the standard chemotherapeutics since their mechanisms of action are unique and cannot be used as substitutes. Moreover, their immunomodulatory outcomes can also be explored further, and this can provide new prospects of stimulating antitumor immune responses. Subsequent interdisciplinary interactions between marine biologists, chemists, pharmacologists and clinicians will be necessary to develop marine bacterial metabolites into clinically useful anticancer agents which will overcome the effects of drug resistance and enhance long-term patient outcome.

8. Discussion

Marine bacterial metabolites constitute a unique and unexploited category of natural products that have a major potential of transforming the sphere of anticancer drug discovery. In comparison to traditional synthetic agents, these compounds are endowed with unmatched chemical diversity, and often have multitargets activities that are more in line with the complicated biology of cancer. The capacity of marine bacterial anticancer agents in inducing apoptosis, disrupting the proteostasis, changing redox state, as well as influencing the tumour microenvironment highlights its therapeutic potential and applicability in overcoming drug resistance.

The translation of marine bacterial compounds into clinical oncology, in spite of these advantages, has not been realised as rapidly as it could have been, with issues of supply, pharmacokinetics, and toxicity being the most prominent. Nonetheless, some of the latest developments in the field of synthetic biology, genome-directed discovery and drug delivery technologies are quickly closing the divide. Notably, this trend of increased interest in the precision medicine approach has emphasised the importance of agents that can address particular molecular vulnerabilities, which is widespread in marine-derived metabolites. Combining mechanistic understanding with novel developmental approaches, marine bacterial anticancer compounds can be implemented successfully in the context of the contemporary therapeutic approaches, especially in the framework of rational combination therapy.

9. Conclusion

Marine microbes provide a source of subsea bacteria that are a rich and largely unexploited source of structurally unique and biologically potent anticancer agents. High diversity of marine bacterial metabolites combined with having the potential to attack a variety of hallmarks of cancer make them a promising next-generation oncology therapeutic option. Emerging and preclinical data show clearly that they are effective in a wide range of cancers, including those with drug resistance, and have a potential to be more selective and have minimal toxicity.

Even though much is yet to be achieved with regard to sustainable production, the complexity of chemicals, and clinical translation, it can be seen that continued progress in the field of genomics, synthetic biology, and computational drug discovery is changing the viability of marine bacterial drug development. These technologies need to be strategically combined, and interdisciplinary work and novel approaches to regulations is necessary to actualize the full therapeutic potential of marine bacterial anticancer agents. Finally, further searching of marine biodiversity of bacteria can provide novel anticancer therapies to complement the existing therapeutic collection and play a significant role in overcoming resistance and enhancing survival of patients in the changing environment of cancer therapy.

List of Abbreviations

AI – Artificial Intelligence ATP – Adenosine Triphosphate CDKs – Cyclin-Dependent Kinases DNA – Deoxyribonucleic Acid EF-1α – Elongation Factor-1 Alpha G1/S – Gap 1 / Synthesis Phase Cell-Cycle Checkpoint G2/M – Gap 2 / Mitosis Cell-Cycle Checkpoint MAPK – Mitogen-Activated Protein Kinase MYC – Myelocytomatosis Oncogene NF-κB – Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells NRPS – Nonribosomal Peptide Synthetase PKS – Polyketide Synthase RiPPs – Ribosomally Synthesised and Post-Translationally Modified Peptides ROS – Reactive Oxygen Species SAR – Structure–Activity Relationship UPS – Ubiquitin–Proteasome System

CRediT authorship contribution statement

Panneerselvam Theivendren: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Conceptualization. **Natarajan Kiruthiga:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Conceptualization. **Surabhi Panneerselvam:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Conceptualization. **Jayakumari Swaminathan.:** Writing – review & editing, Visualization, Validation. **Vijayakumar Murugesan.:** Writing – review & editing, Visualization, Validation. **Kommu Pradeep.:** Writing – review & editing, Visualization, Validation. **Muneer Jan Bhat:** Writing – review & editing, Visualization, Validation, Methodology. **Anna Zarfishan:** Writing – review & editing, Visualization, Validation, Methodology. **Kumarappan Chidambaram:** Writing – review & editing, Visualization, Validation, Methodology.

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Declaration of Competing Interest

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

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Data availability

No data was used for the research described in the article.

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