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Review Article

Marine Actinomycete-Derived Secondary Metabolites for Overcoming Chemoresistance in Cancer Treatment: Focus on Mechanisms and Biosynthetic Pathway

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ABSTRACT

Chemoresistance remains a major limitation of cancer chemotherapy, leading to therapeutic failure, tumour relapse, and poor clinical outcomes. The development of agents capable of sensitising resistant cancer cells or modulating resistance-associated pathways is therefore of considerable pharmaceutical interest. In recent years, marine actinomycetes have emerged as a promising source of structurally diverse secondary metabolites with the potential to interfere with key mechanisms underlying chemoresistance, including drug efflux transporters, dysregulated apoptosis, altered epigenetic regulation, proteasome function, cancer stem cell maintenance, and tumour microenvironment-mediated protection. This review critically summarises current evidence on marine actinomycete-derived secondary metabolites that exhibit chemosensitising or resistance-modulating properties, with emphasis on experimentally validated mechanisms and emerging predictive studies. In addition, the biosynthetic pathways of secondary metabolites, including polyketide synthases, non-ribosomal peptide synthetases, and their hybrids, as well as other unusual enzymes in marine actinomycetes, have been discussed in relation with their cytotoxic potential. Furthermore, recent advances in developing the technologies to identify the available metabolites through genome mining, regulatory engineering, and fermentation optimisation, are highlighted. Key challenges, including intrinsic and translational limitations, are addressed and future perspectives focusing on adapting integrated pharmacological strategies are proposed. Overall, this review has been outlining the broad scope of developing next-generation anti-chemoresistance drugs from the potential substances derived from marine actinomycetes.

Keywords: Antitumour, Bacterial metabolites, Bioactive molecules, Chemoresistance, Chemotherapy, Marine bacteria, Next generation drugs.

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INTRODUCTION

Cancer is a threat to global public health, recording an international value of around 20 million new cases and 9.7 million cancer deaths annually.[1] Surgery, chemotherapy, radiation, hormone therapy and recently developed immunotherapy have significantly reduced the cancer mortality in the last few decades. Chemotherapy aims to stop cell proliferation and block tumour growth; hence, many high-potency chemotherapeutic drugs have been formulated to improve the treatment efficacy. Chemotherapy yields the Objective Response Rate (ORR) ranging from 9.2 to 90.6%, depending on the cancer types.[2] Even though serious side effects are definite, the assessment of the success rate balances these outcomes. Unfortunately, to date, chemotherapy has failed to improve the survival rate of cancer patients who received postoperative chemoradiotherapy.[3] Chemoresistance remains an obstacle to effective chemotherapy as tumor cells develop resistance to therapeutic agents. It has been recorded that over 90% cancer patients under treatment may die due to chemoresistance.[4] Sole or collective mechanisms contributing chemoresistance include epigenetic alterations, gene mutations, and the nature of the Tumour Microenvironment (TME), which may vary among patients.[5] Chemoresistance constitute global challenge, difficult to overcome due to several complex mechanisms, which include adaptive evolution, tumour heterogeneity, TME-associated protective factors, redundancy and pathway plasticity, drug toxicity, poor penetration and drug delivery, and economic deficit associated to manufacturing process.[6,7]

Researchers are now exploring the natural resources to develop eco-friendly, safe remedies in almost every field. Bioactive molecules derived from natural sources have long been proven effective in curing human ailments. To date, scientific reports

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have evidenced that chemically diverse, evolutionarily shaped scaffolds can alter drug efflux and modulate various drug resistance pathways.[8,9] Notably, the marine biomass provides bioactive molecules with unique chemical properties and great potential for cancer treatment.[10] Among oceanic biomass, marine actinomycetes receive great attention due to their peculiar potency to produce new metabolites, including peptides, terpenes, pigments, and fatty acids, which have been shown to exhibit antimicrobial, antioxidant, anti-inflammatory, anti-tumour, and enzyme-inhibitory activities.[11] Salinosporamide A, Thiocoraline, and Adriamycin are a few examples of secondary metabolites derived from marine actinomycetes that possess potential anticancer activities.[12] Sinefungin analogues, neo-actinomycin, and angucyclines derived from *Streptomyces* sp. have been reported to overcome chemoresistance developed in cancer cells.[12] Thus, this review aims to critically analyse current literature on the potential of marine actinomycetes-based metabolites to overcome chemoresistance through various mechanisms. In addition, strategies for enhanced metabolite production, along with the associated limitations, challenges, and future perspectives in this field are discussed to provide a comprehensive overview of their role in anticancer drug development.

Search strategy

A structured literature search was conducted using PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar for articles published up to December 2025. Search terms included combinations of marine actinomycetes, secondary metabolites, chemoresistance, multidrug resistance, cancer, anticancer, biosynthetic gene clusters, genome mining, PKS, and NRPS. Studies were included if they reported marine actinomycete-derived metabolites with anticancer or chemosensitising activity and provided experimental or mechanistic insights into chemoresistance modulation. Articles focusing solely on terrestrial sources, lacking relevance to chemoresistance, or without peer review were excluded. Eligible studies were screened at title, abstract, and full-text levels. Data were synthesised narratively and organised according to resistance mechanisms targeted, metabolite class, and biosynthetic or translational relevance.

Overview of actinomycetes and their secondary metabolites

Actinomycetes are Gram-positive, filamentous spore-formers with high G+C content, which makes them a vital source of bioactive compounds.[13] Due to their extraordinary metabolic activity, actinomycetes can thrive in extreme environments within natural ecosystems, including freshwater, hypersaline soils, deserts, volcanic caves, and limestone. For example, *Frankia* are known for their symbiotic association with actinorhizal plants, supporting nitrogen fixation, producing anti-fungal compounds, and performing ecological functions through the production of secondary metabolites such as calcimycin.[13] According to previous studies, actinomycetes account for over 9% of the marine microbial world and live in distinct niches, including sponges, mangroves, and on the surface of marine macro-organisms.[14]

Marine actinomycetes producing secondary metabolites with antitumor properties

The broad ecological range, metabolic diversity and adaptive strategies of actinomycetes make them a major contributor of secondary metabolite producers with pharmaceutical relevance. To date, around 25,000 microbial secondary metabolites have been discovered, and among those 75% are produced by actinomycetes.[15] Marine species of *Streptomyces, Salinispora,* and *Marinispora* biosynthesise polyketides, including Actinofuranones, Chalcomycin, Nonactin, Marinomycin A and many others with potential cytotoxic and anticancer activities.[16] *Streptomyces* sp. ROA-065, isolated from marine sediments, produced homiamides A, B, and C, classified as depsipeptides, possessing anti-bacterial and immunomodulatory effects. Ester and peptide bonds in these non-ribosomal peptides exhibit unique structural features and confer cytotoxic and antitumour efficacies.[17] Halogenated alkaloids, isotirandamycin B, imidazole, indolizidines, piperidines, and pyrimidines are a few among 77 discovered alkaloids of marine actinomycetes.[18] Isoprenoid and indocarbazole compounds derived from *Streptomyces* and *Actinomadura* sp. have rarely been reported to exhibit antitumour activity in cancerous colon, leukaemia, and breast cancer cell lines.[16] Marine actinomycetes are recognised for their enzyme inhibitors, which can degrade aliphatic compounds and hydrocarbons. *Streptomyces* has been considered the major actinomycete due to the abundance of bioactive products. Around 140 natural products, including jejucarboside A41 and several saturated acyl compounds, have been isolated from *Steptomyces* sp.[19,20] When considering the actinomycete richness in the ocean, we explored only a small number of bioactive molecules. Figure 1 shows the structures of several secondary metabolites with antitumour properties as reported in the earlier studies.

An overview of chemoresistance against current chemotherapeutic drugs

Chemoresistance in cancer continues as a global barrier to the effective treatment of all types of cancer, and this causes tumour recurrence and metastasis. Thus, understanding the complex, multifactorial mechanisms underlying chemoresistance is crucial for developing a novel anticancer drug. This section provides a summary of interconnected chemoresistance mechanisms encompassing oncogenes, transporter pumps, inactive tumour suppressor genes, enhanced DNA repairing, macropinocytosis and autophagy, exosomes, mitochondrial alterations, Epithelial-Mesenchymal Transition (EMT), cancer stem cells, epigenetic modifications, tumour microenvironment, and metabolic reprogramming. Thus, this is an interplay of cellular,

metabolic, and genetic processes that motivates cancer cells to adapt and thrive under chemotherapy-induced stress.[21] This section reviews the key mechanisms of chemoresistance and their role in reducing the effectiveness of anticancer therapies.

The rate of glucose metabolism in cancer cells is always high to meet the energy requirements of high proliferation, which may be a common cause of cisplatin (antitumour drug) resistance. Cancer cells may upregulate glycolytic enzymes, acetyl-CoA inhibitors, GLUT1, and monocarboxylate transporters, all of which inhibit the suppression of glycolysis.[22] Urothelial bladder cancer cell lines that underwent cisplatin treatment developed resistant sublines due to high glucose uptake and GLUT3 expression.[23] Activation of supportive pathways, including the Pentose Phosphate Pathway (PPP), in association with glycolytic activity causes metabolic impairment and compositional changes in the cell membrane, which reduces cisplatin uptake.[22] The taxane resistance mechanism is unique to cancer type, in which upregulated HlF1-α, pro-survival pathways (mTOR and p13K), drug-metabolising enzymes, transporters, and many other mechanisms act in concert.[24] Alalawy *et al*.,[25] reported upregulation of drug resistance genes, including EDIL3, MRP1, ABCB1, and CSAG2/TRAG-3 in paclitaxel-resistant phenotypes. Elevated expression of long non-coding RNA H19 (lncRNAH19), downregulation of the pro-apoptotic pathway and prevention of cancer cell death have been reported in paclitaxel-resistant breast cancer cases. Doxorubicin, one of the leading drugs used in chemotherapy, is emerging as a resistant drug due to the autophagy-mediated lysosomal degradation. This process inhibits apoptosis and remodels the metabolic activity of cancer cells, and enhances carcinogenesis.[26] Lung cancer cells show resistance to chemotherapy with 5-Fluorouracil (5-FU) by the altered TME and immune-related NOTCH and WNT/β-catenin signalling.[27] The anti-tumour activity of marine actinomycete-derived secondary metabolites and the mechanisms to overcome the chemoresistance, along with the IC_{50} values, are provided in Table 1. To date, many studies have identified the molecular mechanisms underlying chemoresistance exerted to commonly used potential anticancer drugs. This fundamental knowledge is guiding us in developing novel anticancer drugs from natural sources, a field that encounters significantly less resistance, as observed from the earlier studies.

Actinomycete-derived metabolites that reverse or overcome chemoresistance

Inhibitors of drug efflux pumps

Increased activity of drug efflux pumps, a metabolic process that drives chemoresistance. Enhanced efflux increases ATP-Binding Cassette (ABC) superfamily, motivates DNA repair, modifies the metabolism or detoxification, suppresses the expression of apoptosis-associated protein Bcl-2 and tumour suppressor proteins, and decreases drug influx. Among these, the hyperactive ABC superfamily, including P-glycoprotein (P-gp/ABCB1), Breast Cancer Resistance Protein (BCRP/ABCG2), and Multidrug Resistance-associated Protein 1 (MRP1/ABCC1), drives out the chemotherapeutic agents outside the cancer cells, thereby decreasing the intracellular accumulation and efficacy of anticancer drugs.[55] Staurosporine, an indolocarbazole alkaloid produced by *Streptomyces*, enhances the accumulation of vincristine in Multi-Drug-Resistant (MDR) cells through the azidopine photolabeling system of P-gp. The binding of staurosporine to P-gp and anti-cancer drugs, by blocking the Ca_2+ channels, acts as an inhibitor of the drug efflux pump.[51] An *in silico* study by Ghandadi demonstrated that the *Salinispora*-derived compounds, saliniquinones, cyanosporoside, and cyclomarazine, exhibited inhibitory efficacy against ABC transporters, especially P-gp, thus inhibiting drug efflux pumps and offering therapeutic scope in MDR cancer cells.[38]

Inducers of apoptosis or blockers of survival pathways

Tumour cells violate the cellular checkpoints by overexpressing the anti-apoptotic proteins of Bcl-2 family (BCL-2, BCL-X_L, BFL-1, BCL-W, and MCL-1), maintain mitochondrial integrity, thereby developing MDR cancer cells. Hence, bioactive compounds targeting these pro-apoptotic parameters by disrupting survival signalling pathways cause cancer cell death, leading to a successful cancer treatment. Bcl-2 mitochondrial proteins, especially Bcl-X_L are resistant to a wide range of anti-cancer drugs. Computational molecular docking analysis showed that antimycin A, an actinomycete alkaloid, interacts with Bcl-2 domain of Bcl-X_L and inhibits anti-apoptotic protein expression.[52] The above study reveals the influence of antimycin A on mitochondrial apoptotic pathway and cell cycle regulation, providing scope for a therapeutic agent against p53-associated tumours.[53] *Streptomyces* sp. THS-55-derived antimycin (N-acetyl-deformylantimycin A) degrades HPV E6/E7 oncoproteins through ROS-dependent ubiquitin-proteasome pathway, leading to cell cycle inhibition and triggers apoptosis in cervical cancer cells.[54]

DNA-targeting or DNA-damaging metabolites

Thiocoraline, a non-ribosomal peptide derived from the marine *Micromonospora marina*, demonstrated anti-tumour activity by blocking the cell cycle at the G1 step. Interaction of Thiocoraline with DNA polymerase α inhibits the DNA elongation process and inhibits DNA replication, which declines the progression of the cell cycle to the S phase in LoVo and SW620 human colon cancer cell lines.[55] Rebeccamycin, an indolocarbazol alkaloid produced by *Lechevalieria aerocolonigenes* arrests the cell cycle in lung adenocarcinoma cells by inhibiting DNA topoisomerase I and induces apoptosis.[39] Unfortunately, clinical trials of rebeccamycin have not progressed beyond phase II due to its low water-soluble nature. Inhibition of the ubiquitin-proteasome system can be a therapeutic measure in treating glioblastoma. Salinosporamide

A, also known as Marizomib, is a natural γ-lactam-β-lactone compound produced by *Salinispora tropica*, that inhibits the catalytic subunits of 20S proteasome and leads the cancer cells to apoptosis.[46]

Epigenetic modulators

A major mechanism by which tumour suppressor genes repress cancer is epigenetic silencing, which leads to chemoresistance, immune depression, and cancer progression. Epigenetic modulators restore histone acetylation or reverse DNA methylation, thereby reactivating tumour suppressors such as CDKN2A/p16, DAPK, MLH1, and sensitising tumour cells to cancer therapy.[56] Sinefungin and its derivatives, derived from *Streptomyces* sp. possess DNA Methyltransferase inhibiting (DNMT) efficacy, offering a potential epigenetic effect.[29] *Streptomyces* are rich in Histone Deacetylase (HDAC) inhibitors, extensively used as epigenetic probes. For instance, Trichostatin A, derived from *S. hygroscopicus*, restores histone acetylation and reactivates tumour suppressor genes and cell cycle regulators. *In silico* docking studies revealed that marine *Streptomyces*-derived heliomycin and tetracenomycin D showed HDAC activity in microbiological and biochemical assays.[57] and their potency and selectivity can be standardised.

Metabolites modulating tumour microenvironment

TME is an active contributor to cancer progression, composed of endothelial cells, vasculatures, mixed cell types (CAF, TAM, MDS, T-cells), matrix, and soluble factors that promote drug-resistant tumour growth. Actinomycetes-derived secondary metabolites reverse the TME by modulating immunosuppression/TME inflammation and suppressing angiogenesis.[58] Nathan and Kannan reported the anti-chemoresistance efficacy of secondary metabolites through anti-angiogenic and signalling inhibition, including endothelial proliferation, migration, downstream kinases, and VEGF/VEGFR factors.[36] Choi *et al.*,[47] demonstrated the anti-angiogenic efficacy of Lucknolide A, isolated from the marine *Streptomyces strain*, by inhibiting VEGF in *ex vivo* assays. By interrupting the $VEGFR_2$ pathway, Lucknolide A induces endothelial generation and microvessel formation, reducing vascularisation and normalising leaky vessels to improve drug delivery and drug sensitivity. Cytokine-driven survival signalling (contributed by IL-6/STAT3, and TNFα/NF-κB), accumulation of immunosuppressive cells and remodelled extracellular matrix contribute to the inflammatory or immunomodulatory TME. Rapamycin, found in *S. hygroscopicus*, alters pro-inflammatory cytokine signalling, thereby altering the composition of immune cells in TME.[44] Immunologically, the mammalian Target of Rapamycin (mTOR) signalling pathway is the key regulator of immune responses in TME.[59] This actinomycete-derived TME-modulating agent enhances the chemotherapy sensitivity in various preclinical studies.

Modulators of Cancer Stem Cells (CSCs) and Epithelial-Mesenchymal Transition (EMT)

CSCs and EMT are interlinked processes that play a crucial role in metastasis and chemoresistance. CSCs self-renew and maintain tumour-initiating capability by expressing markers such as CD44, SOX2, ALDH1, LGR5, OCT4, and Nanog, to thrive under cytotoxic stress. On the other hand, EMT is characterised by migration and invasiveness as cells gain stem-like properties. Salinomycin, a potassium ionophore, inhibits Wnt/β-catenin signal transduction pathway, which is crucial for stem cell development. Salinomycin interferes with LRP6 phosphorylation and suppresses the Wnt target genes, fibronectin, LEF1, and cyclin D1, and kills the transfected HEK293 cells.[60] Salinomycin-mediated suppression of Wnt/β-catenin signalling and Hedgehog pathway activity downregulates the stemness markers in chronic lymphocytic leukaemia cells.[60] Though various studies reported the extraction of Salinomycin, an anticoccidial polyketide, from *S. albus*, no studies are available on the anti-chemoresistance efficacy of marine actinomycetes-based derivatives. Aureolic acids, such as mithramycin and chromomycins, are reported to suppress the expression of stemness markers, reduce sphere formation, inhibit CSC survival, prevent EMT, and induce immunogenic cell death in various cancer cells.[61,62] However, studies dealing with the anti-tumour efficacy of marine actinomycete derivatives of these molecules are scarce.

New or underexplored metabolites identified via genome mining/metabolomics

The traditional way of random screening to identify the bioactive molecules has now been transformed into a target-informed pharmacological exploration method, such as genome mining. The nuclear genome of actinomycetes may not be encrypted for its rich source of bioactive compounds, including peptides (ribosomal and non-ribosomal) and polyketides. The metabolic pathways for the synthesis of these compounds are encoded in Biosynthetic Gene Clusters (BGCs), which may be transcriptionally silent and thus represented as underexplored pharmacophores. Adapting *in silico* methods, BiG-SCAPE/GNPS and antiSMASH with metabolomics can aid in the lower-abundant metabolites coding for BCG.[63] In a recent study, 4098 Ribosomally synthesised post-translationally modified peptides (RiPPs) were found using BAGEL and anti-SMASH mining tools.[64] GNPS molecular networking, NMR confirmation, and adenylation/substrate analysis provide early insight into the biosynthesis, biochemical functionality, and expected molecular targets, helping to prioritise the compounds with properties needed to develop a drug.

Biosynthetic pathways of key anti-chemoresistance metabolites

Genomic surveys using advanced bioinformatics tools revealed a high density of BGCs, encoding the synthesis of Polyketide

Synthases (PKS), Non-Ribosomal Peptide Synthetases (NRPS), and their hybrids, as well as unusual enzymes in marine actinomycetes. Marine *Streptomyces, Salinispora*, and *Micromonospora* produce polyketides with antiangiogenic and chemosensitizing efficacies via enzymatic assembly by PKSs and PKS-NRPS megasynthases. The resulting long, diverse polyketide backbones are further enriched by glycosyltransferases, oxygenases, and halogenases, thus representing a unique source of novel pharmaceuticals.[11]

Adaptive features in marine actinomycetes to cope with extreme environments enable the production of extemozymes with unique structural motifs that target cellular uptake, target engagement, and resistance profiles of tumour cells.[65] Salinosporamide A, also known as marizomib, is primarily produced by *S. tropica* and *S. arenicola*. Salinosporamide BGC encodes a biosynthetic pathway, which employs β-lactone-γ-lactam production and crotonyl-CoA carboxylase/reductases to build up a four-carbon pharmacophore. Enzyme-mediated structural modification forms bicyclic β-lactone, which plays a crucial role in proteasome inhibition.[66] Irreversible inhibition of the 20S proteasome induces proteotoxic stress and apoptotic signalling that helps to overcome resistance by conventional chemotherapies.[46]

PKS pathways

Marinomycin, which belongs to the Type I PKS system, is encoded by a ~72 kb large BGC.[67] Marinomycins exhibit a unique mode of action to form polyketide dimerisation and photo/chemical reactivity that demonstrates selective cytotoxicity

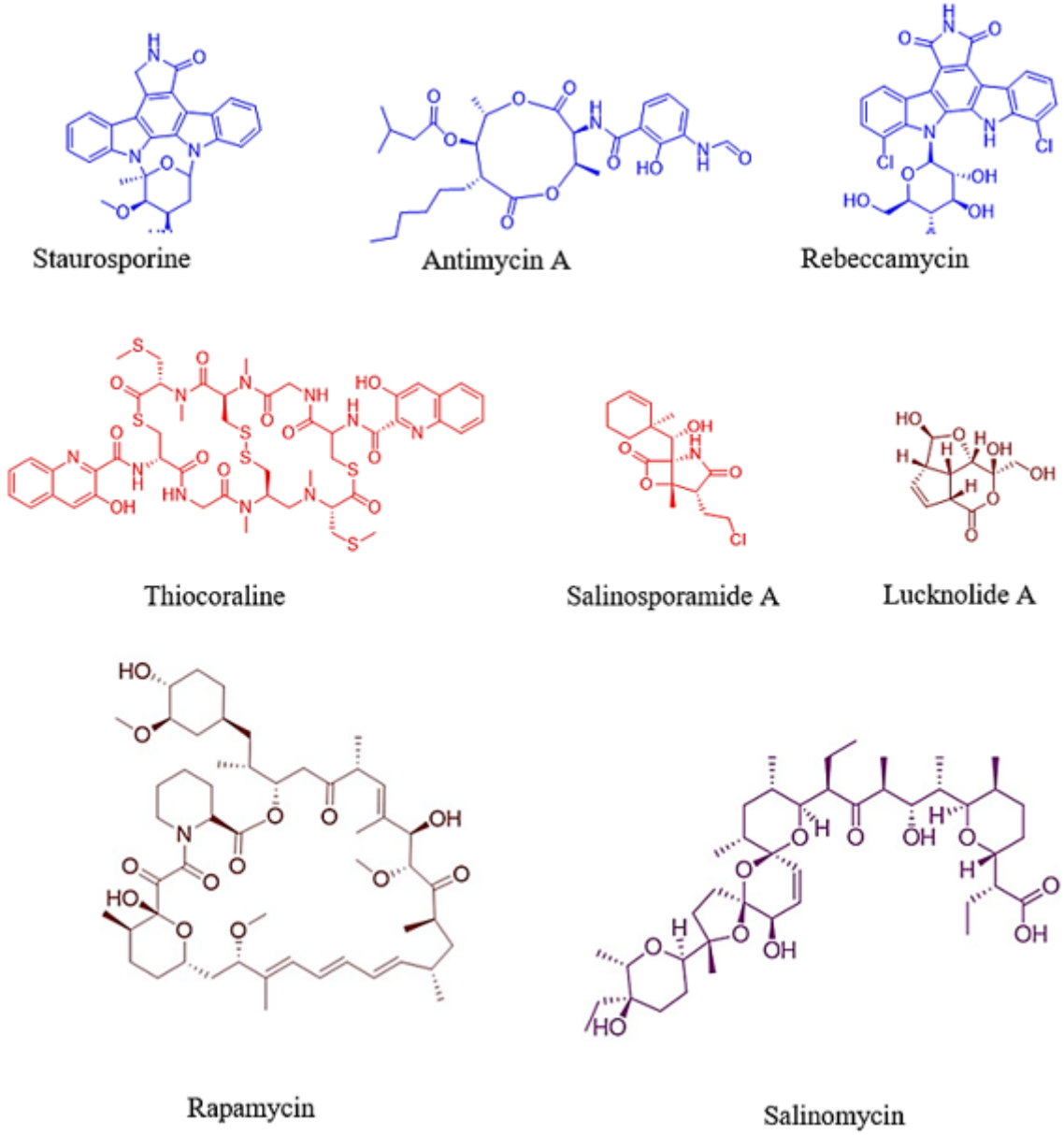

Figure 1: Structure of potential actinomycetes-derived secondary metabolites possessing anti-chemoresistant antitumor efficacy.

Table 1: Anti-tumour activity of secondary metabolites found in the marine actinomycetes.

Secondary metabolites	Source Actinomycete species	Anti-chemoresistance mechanism	Important observations (IC_{50}/Cell Line/*In vivo*)
Carpatamides A-C[28]	*Streptomyces* sp.	Cytotoxicity	IC_{50} of 2.8 µM in HCC366 4.1 µM in A549 8.4 µM in HCC44
Sinefungin analogues[29]	*Streptomyces* sp.	Inhibition of histone methyltransferases EHMT1 and EHMT2 Reversing repressive chromatin states related to drug resistance Epigenetic modulation.	IC_{50} of ≈ 1.5 - 103 µM in biochemical assay
PM100117 PM100118[30]	*Streptomyces caniferus* GUA-06-05-006A	Plasma membrane disruption - rapid necrotic death Induce apoptosis resistance mechanisms.	LC_{50} values of 3.8 and 4.1 µM HT29 cells
Neo-actinomycin A[31]	*Streptomyces* sp. IMB094 (marine sediment)	DNA intercalation Inhibition of transcription Overcoming repair-mediated resistance.	IC_{50} of 38.7 nM in HCT116 CRC cells
ULDF4 (staurosporine) ULDF5 (staurosporine)[32]	*Streptomyces bingchenggensis* ULS14	Induce apoptosis Overcome survival/adaptive resistance mechanisms.	IC_{50} in HeLa cell line 0.034 µg/mL for ULDF4 0.075 µg/mL for ULDF5
Dionemycin 6-OMe-7′,7″-dichlorochromopyrrolic acid[33]	*Streptomyces* sp. SCSIO 11791 (deep-sea)	Cytotoxicity via bis-indole scaffold DNA interaction/Apoptosis induction Influence halogenation Mechanism not fully detailed.	IC_{50} range of 3.1-11.2 µM in NCI-H460, MDA-MB-231, HCT-116, HepG2.
Furan-type compounds[34]	*Streptomyces* sp. VN1	Inhibits cancer cell growth Reduces migration/invasion Targets pro-metastatic/chemoresistant behavior.	IC_{50} of 40.5 µM in AGS 123.7 µM in HCT116 84.67 µM in A375M 50 µM in U87MG 58.64 µM in A549
Sharkquinone Resistomycin Undecylprodigiosin Butylcyclopentylprodigiosin Elloxizanone A and B Carboxyexfoliazone Exfoliazone[35]	*Streptomyces* sp. EGY1 (marine sediment)	Apoptosis induction Restores sensitivity to TRAIL via downregulation of XIAP and survivin.	IC_{50} of ~65.5 µM in HCT116 IC_{50}~24 µM in MDA-MB-231
Streptopyrrolidine Cyclo-(L-Pro-L-Met) Streptochlorin Lynamicins Thiocoraline[36]	*Streptomyces* sp. KORDI-3973 *Nocardiopsis* sp. 03N67 *Streptomyces strain* 04DH110 *Marinispora* sp. NPS12745 *Micromonospora* sp. L-13-ACM2-092	Inhibition of endothelial tube formation Anti-angiogenic activity Induction of ROS-mediated apoptosis; Downregulation of VEGF; Inhibition of NF-κB Anti-angiogenic activity and reduction of ABCG2-mediated resistance Cytotoxicity; anti-angiogenic efficacy.	Inhibition of HUVEC tube formation *in vitro* Inhibition of HUVECs in human umbilical vein endothelial cells IC_{50} ~1.05 µg/mL In K-562 Cytotoxicity in MEL-288, A549, P388 models

Secondary metabolites	Source Actinomycete species	Anti-chemoresistance mechanism	Important observations (IC_{50}/Cell Line/*In vivo*)
Lu01-M[37]	*Streptomyces* sp. (Marine sediment)	Apoptosis induction Necroptosis ER stress Cell cycle G2/M arrest DNA damage Proliferation and migration inhibition.	IC_{50} values of 1.03±0.31 µg/mL in PC3 2.12±0.38 µg/mL in DU145 1.27±0.25 µg/mL in LNCaP
Saliniquinones Cyclomarazine Cyanosporoside A[38]	*Salinispora* sp.	Predicted inhibition of ABC efflux transporters Predicted modulation of ABC transporter function Predicted modulation of ABC transporter function.	-
Rebeccamycin[39]	Lentzea aerocolonigenes	DNA intercalation Topoisomerase inhibition Improved drug availability.	No direct IC_{50} reported
Kendomycin B-D[40]	*Verrucosispora* sp. SCSIO 07399	DNA damage Proteasome impairment Apoptosis induction.	IC_{50} ~2.2-44 µM in MGC-803, A549, HeLa, HepG2, MCF-7, RKO cell lines
4H-Chromen-4-one derivative[41]	*Streptomyces ovatisporus* S4702T	Apoptosis induction Cell proliferation inhibition.	EC_{50} of ~9.68 µg/mL in colon carcinoma ~9.93 µg/mL in prostate adenocarcinoma
Cyclo(Pro-Ala) Cyclo(Pro-Phe) Cyclo(Pro-Val) Cyclo(Pro-Leu)[42]	*Streptomyces* sp. IMB094 (rhizosphere soil in the mangrove *Avicennia marina*)	DNA interaction Apoptosis induction.	IC_{50} of 47.6, 32.3, 67.2, and 92.6 µg/mL, respectively
Angucyclines: Mayamycin A and B Rabelomycin[43]	*Streptomyces* SCSIO LCY30	Cytotoxicity induced by DNA damage/ apoptosis Overcome survival-pathway-linked resistance Reversal of repair-based resistance.	IC_{50} values of 0.60-2.22 µM in MDA-MB-231, MDA-MB-468, and Bt-549 cell lines
Rapamycin[44]	Streptomyces hygroscopicus	Suppression of PI3K/Akt/mTOR survival pathway Autophagy Induction Reversal of resistance linked to aberrant growth-factor signalling Inhibition of mTORC1 signalling.	IC_{50} value in low-nanomolar range *in vitro* and *in vivo* (MCF-7; PC-3; U87)
Oligomycin compounds[45]	*Streptomyces* sp. FXY-T5	Arrest G1-phase cell cycle arrest Attenuate Cyclin D1 and PCNA expression through a β-catenin signaling pathway.	IC_{50} values less than 10 µM in DLD-1 cells

Secondary metabolites	Source Actinomycete species	Anti-chemoresistance mechanism	Important observations (IC_{50}/Cell Line/*In vivo*)
Salinosporamide A (Marizomib)[46]	Salinispora tropica	Irreversible inhibition of human 20S proteasome Accumulation of misfolded proteins Increased ER stress Apoptosis induction.	IC_{50} for various β catalytic sites 18.5 nM for β5 326.5 nM for β2 596.6 nM for β1 GI_{50} of ~10 nM across NCI60 ~10-35 nM in HCT116.
Lucknolide A[47]	*Streptomyces* sp. strain 151KO-065	VEGF/$VEGFR_2$ signalling inhibition Suppression of $VEGFR_2$ and downstream effectors Cell cycle arrest Inhibition of migration, tube formation and microvessel sprouting.	CC_{50} for endothelial proliferation in EA.hy926: ~29.86 µM (no VEGF) ~15.46 µM (with VEGF) CC_{50} for endothelial proliferation of HUVEC ~40.41 µM (no VEGF) ~29.35 µM (with VEGF).
Rapamycin[48]	Streptomyces hygroscopicus	Exhibits binding to oncogenic receptors involved in proliferation, survival, and resistance pathways (EGFR, MET, FGFR, ROS1 and ALK).	*In silico* study showed binding affinities of 8.8 kcal/mol for EGFR 8.3 kcal/mol for MET 8.1 kcal/mol for FGFR 7.7 kcal/mol for ROS1 7.5 kcal/mol for ALK Higher cytotoxicity in A549 cells.
Cis-9-Octadecenoic acid[49,50]	*Streptomyces* sp. 22SH (Marine sediments)	Anti-topoisomerase activity Induction of apoptosis Interruption of proliferation pathways.	IC_{50} of 17.48±0.94 µg/mL in HepG2 88.73±4.78 µg/mL in MCF-7 IC_{50} of Topoisomerase I inhibition 0.65±0.023 µg/mL.

against cancer cells. Investigations on marinomycin are scarce due to its heterologous expression in the biosynthetic machinery of the marine *Marinispora*.[68] Xu *et al.*,[69] described the biosynthesis of angucyclines and angucyclinones from the marine actinomycetes. Unique marine-specific properties of these compounds are produced through the type II PKS pathway tailored by halogenases and glycosyltransferases. Cytotoxic analogues in angucyclines, including redox cycling, intercalation, and topoisomerase inhibition, can modify the efflux susceptibility of MDR cancer cells.[70]

PKS-NRPS hybrid pathways

Peptide and peptide-polypeptide hybrid scaffolds synthesised via NRPS pathways execute the novel cellular process in resistant cancer cells. Hybrid megasynthetases incorporated with polyketidic motifs such as enediynes, glycopeptides, and bleomycin-type compounds are the canonical examples of hybrid NRPS/PKS anticancer agents. Bleomycin exhibited DNA-scission warhead anti-cancer activity, but no studies are available for marine actinomycetes-derived bleomycin. Kendomycin, an unusual ansa-type macrolide is produced by the type I and III

PKS biosynthetic pathway in *Verrucosispora* sp.[40] Structurally complex kendomycin exhibits DNA interaction and off-target toxicity in tumour cell lines. Understanding the kendomycin BGC architecture in *Verrucosispora* sp. and its role in sensitising cancer drug uptake would scale up the pharmacological optimisation of this compound.

Regulatory networks controlling biosynthesis

Secondary metabolite production in marine actinomycetes is controlled by multi-layered regulatory networks integrated with pathway-specific (BGC-specific) regulators and other global (pleotropic) regulators. By manipulating these networks, including altering BGCs, increasing the yield of desired compounds, as well as generating novel analogues, it is possible to bring desired anti-chemoresistance capabilities into the focus of pharmacological evaluation.[71] Pathway-specific regulators are Cluster-Situated Regulators (CSR) types, including TetR, LAL, LysR, MarR, SARP (*Streptomyces* antibiotic regulatory protein), PAS-LuxR, and others. These regulators directly control the biosynthesis and resistance transcriptional pathways, which target the product formation.[72] Global regulators comprise several transcriptional factors, proteins, and signalling molecules that control cellular metabolism, morphology, and stress responses that affect BGCs. Modulation of global regulators helps to uncover silent gene clusters and reveal novel compounds, therefore attractive for natural-product discovery projects.[72]

Strategies to enhance production of anti-chemoresistance metabolites

Lower production of metabolites, silent BGCs, and poor accessibility of compounds due to insufficient laboratory methods are the current issues hindering the pharmacological development of anti-chemoresistance metabolites. To overcome the challenges, adaptation of modern technologies to improve screening and selection based on good traits, bacterial culturing, and metabolite biosynthesis is necessary. A recent study by Hu *et al.*,[73] demonstrated that optimisation of fermentation conditions, such as duration, seed age, ratio and volume of inoculum, and pH, can increase the yield of Chrysomycin A from *Streptomyces* sp. 891-B6. Incorporation of optimisation and One Strain-Many Compound (OSMAC) concept is one among the many approaches to unlock the silent BGCs. To overcome the lengthy experiment duration in OSMAC, co-cultivation and the integration of microbiological, computational, and technological approaches are adapted, according to Romano *et al.*,[74] Co-cultivation is among the most familiar elicitation methods, in which the co-culture of *Rhodococcus* UR59 and *Actinokineospora spheciospongiae* EG49 isolated from the Red Sea yielded enhanced production of secondary metabolites, including angucyclines.[75] Similarly, co-cultivation of the marine sponge-derived *Actinokineospora* sp. EG49 and *Micromonospora* sp. UR56 produced metabolites with cytotoxic activities, which were not traced in its solo culture.[76] Co-cultivation of marine actinomycetes with fungal and tropical plant elicitors enhances the expression of genes encoding various metabolites and regulators.[77] Additionally, chemical

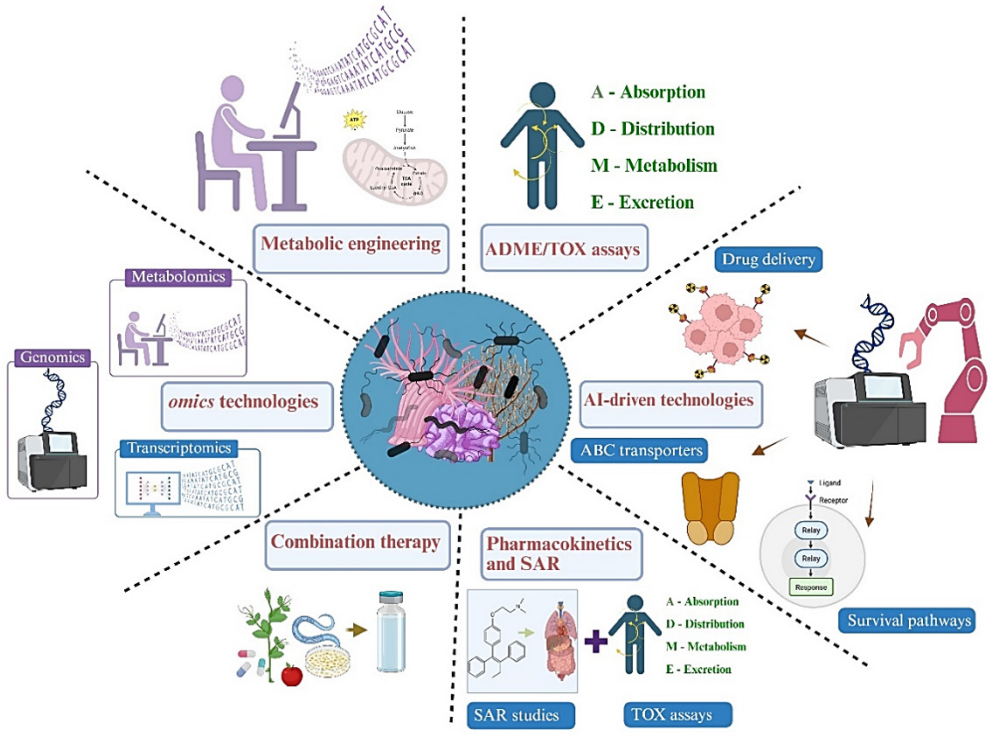

Figure 2: Future perspectives for the development of anti-chemoresistance therapeutics from marine actinomycete-derived secondary metabolites.

and molecular elicitation-enhanced secondary metabolite biosynthesis has emerged as successful in recent years.

CHALLENGES AND LIMITATIONS

The broad chemical diversity and potential anti-chemoresistance efficacies of marine actinomycetes-based secondary metabolites are limited by both intrinsic and translational challenges. As in any natural product yield, secondary metabolite production faces low titers, which also affect ADME (Absorption, Distribution, Metabolism, Excretion) as well *in vivo* performance of the compounds. Most of the time, molecular elicitation methods are needed to activate the silent BGCs, but these approaches are not universally effective at present.[78] Efficient production and chemical optimisation are more challenging for complex, polycyclic structures, though these features possess unique biological activity. Risks in SAR (structure-activity relationship) exploration act as barriers in improving pharmacokinetic profiles of metabolites.[79] Incidence of off-target toxicities can be understood only if large quantities of metabolites are available. ADME/Tox profiling and safety assessments are necessary to avoid hazards during preclinical development. The translational gap between *in vitro* bioactivity and *in vivo* efficacy has been validated to solve the unacceptable efficacy or toxicity issues arising from TME, immune interactions, and drug-delivery barriers.[80] Moreover, understanding the mechanism of action behind reverse chemoresistance has been partially elucidated, but there is still more to explore. Bridging these gaps by adapting integrated pharmacology strategies helps to improve the therapeutic properties of unique actinomycete compounds.

FUTURE PERSPECTIVES

The development of discovery and investigations on potential anti-chemoresistant metabolites from marine actinomycetes is accelerated by innovative technologies. Integrated advancements in the field of genomics, metabolomics, and transcriptomics (omics technologies) facilitate the identification of uncharacterized BGCs, especially the genetic determinants for their structural motifs. Predicting metabolite structure from datasets using integrated metabolomics and genome mining would simplify appropriate bacterial isolation and compound biosynthesis among the complex microbiomes.[81] Integrated artificial intelligence, machine learning algorithms, along with omics technologies, can speed up the structure prediction and dereplication of novel compounds. Moreover, the adaptation of downstream ADME/Tox assays helps save cost and time in drug discovery. Metabolic engineering approaches to alter the metabolic pathways, deleting or suppressing competing pathways, and generating engineered strains with optimised energy metabolism, in the aim of enhancing pharmacological characterisation, would scale up the production.[82] Pharmacokinetic studies and SAR campaigns practice adding biosynthetic precursors such as malonyl-CoA to boost the metabolite titres. Apart from enhancing the production process, bio-transformation approaches modify the analogues of the products with improved pharmacological profiles.[82] Predictive mechanistic models are constructed using AI and trained based on the curated datasets to prioritise natural products relevant to chemoresistance, including ABC transporters, survival pathways, and many other. This *in silico* matching would ease the finding of high-value leads.

The concept of combination therapy would always be worthy, even successful in nanomedicine. Exploring rational combinations including chemotherapy (cisplatin, doxorubicin) and natural products based on their mode of action has strong translational value, particularly when monotherapy fails. Emerging trend of personalised oncology fears the scope of application of natural products as well; hence personalised interventions using AI-adapted multi-omics approaches enable clinicians to select mono- or combinational therapies based on the patient profile. These personalised strategies align with patient-specific chemoresistance profiles and enhance response rates with diminished adverse effects.[83] Figure 2 illustrates the key research priorities for developing anti-chemoresistance therapeutics.

CONCLUSION

Chemoresistance poses a significant challenge in cancer chemotherapy, influenced by complex and interconnected mechanisms. The bioactive potential of secondary metabolites found in the marine actinomycetes in inhibiting multi-complex mechanisms underlying the chemoresistance of cancer cells highlights their unique pharmacological value. Despite encouraging preclinical findings, challenges concerning scalability, pharmacokinetics, safety, and clinical translation persisted. Addressing these restrictions through integrated and multidisciplinary strategies, incorporating individualised and combined medicines, will be crucial for their effective clinical implementation. Overall, the present review aimed to insist the development of next-generation anti-chemoresistance agents from marine actinomycetes.

ABBREVIATIONS

ABC: ATP-binding cassette; **ABCB1:** ATP-binding cassette subfamily B member 1 (P-glycoprotein); **ABCC1:** ATP-binding cassette subfamily C member 1; **ABCG2:** ATP-binding cassette subfamily G member 2; **ADME:** Absorption, Distribution, Metabolism and Excretion; **AI:** Artificial Intelligence; **ALK:** Anaplastic Lymphoma Kinase; **ATP:** Adenosine Triphosphate; **BCL-2:** B-cell Lymphoma 2; **BCL-XL:** B-cell Lymphoma-Extra Large; **BCRP:** Breast Cancer Resistance Protein; **BGC:** Biosynthetic Gene Cluster; **CAF:** Cancer-Associated Fibroblast; **CSC:** Cancer Stem Cell; **CSR:** Cluster-Situated Regulator; **DNA:** Deoxyribonucleic Acid; **DNMT:** DNA Methyltransferase; **EC_{50}:** Half Maximal Effective Concentration; **EGFR:** Epidermal Growth Factor Receptor; **EHMT1/EHMT2:** Euchromatic Histone-Lysine

N-Methyltransferase 1/2; **EMT:** Epithelial-Mesenchymal Transition; **ER:** Endoplasmic Reticulum; **FGFR:** Fibroblast Growth Factor Receptor; **GI_{50}:** 50% Growth Inhibition Concentration; **GLUT:** Glucose Transporter; **HDAC:** Histone Deacetylase; **HEK293:** Human Embryonic Kidney 293 Cells; **HIF-1α:** Hypoxia-Inducible Factor 1 Alpha; **HPV:** Human Papillomavirus; **HUVEC:** Human Umbilical Vein Endothelial Cells; **IC_{50}:** Half Maximal Inhibitory Concentration; **IL-6:** Interleukin-6; **lncRNA:** Long Non-Coding RNA; **MDR:** Multidrug Resistance; MDS: Myelodysplastic Syndrome; **MET:** Mesenchymal Epithelial Transition Factor; **mTOR:** Mammalian Target of Rapamycin; NF-κB: Nuclear Factor Kappa B; **NRPS:** Non-Ribosomal Peptide Synthetase; **ORR:** Objective Response Rate; **OSMAC:** One Strain Many Compounds; **PCNA:** Proliferating Cell Nuclear Antigen; **PI3K:** Phosphoinositide 3-Kinase; **PKS:** Polyketide Synthase; **PPP:** Pentose Phosphate Pathway; **RiPPs:** Ribosomally Synthesized and Post-Translationally Modified Peptides; **RNA:** Ribonucleic Acid; **ROS:** Reactive Oxygen Species; **SAR:** Structure-Activity Relationship; **SARP:** *Streptomyces* Antibiotic Regulatory Protein; **STAT3:** Signal Transducer and Activator of Transcription 3; **TAM:** Tumor-Associated Macrophage; **TME:** Tumor Microenvironment; **TNF-α:** Tumor Necrosis Factor Alpha; **TRAIL:** TNF-Related Apoptosis-Inducing Ligand; **VEGF:** Vascular Endothelial Growth Factor; **VEGFR:** Vascular Endothelial Growth Factor Receptor; **WNT:** Wingless-Related Integration Site.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

SUMMARY

Chemoresistance contributes to treatment failure, tumour recurrence, and poor prognosis in cancer treatment. This review comprehensively examines marine actinomycete-derived secondary metabolites as promising agents for overcoming chemoresistance. It summarises the multifactorial mechanisms underlying resistance and highlights the modulation of signalling pathways using structurally diverse metabolites from marine actinomycetes. In addition, advances in genome mining, metabolomics, and biosynthetic gene cluster analysis are discussed as strategies to identify underexplored metabolites. Challenges related to low yields, pharmacokinetics, off-target toxicity, and translational gaps are critically addressed. Collectively, the review underscores the potential of marine actinomycete-derived metabolites as adjuncts to conventional chemotherapy and as leads for the development of next-generation therapeutics against chemoresistance.

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