African Journal of Physics, Chemistry, and Medical Laboratory Science (AJPCMLS)
E-ISSN 2978-3348 (Online); ISSN 2978-333X (Print)

Indexed by SABINET and EBSCO

Volume 1, Number 1, December 2025

Pp 9-32

Marine Natural Products in the Omics Era: Integrative Approaches for Drug Discovery and Biomedical Innovation

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Abstract

Marine natural products have long been fundamental to modern drug discovery, particularly due to the exceptional structural diversity and potent pharmacological profiles of marine metabolites. The advent of genomics, transcriptomics, proteomics, and metabolomics—collectively known as omics technologies—have transformed the investigation of marine natural products by enabling rapid dereplication, accurate biosynthetic pathway elucidation, and efficient identification of bioactive compounds. This review discusses the contribution of marine-derived metabolites to contemporary drug discovery, highlighting their anticancer, antimicrobial, antiviral, and anti-inflammatory potential. Particular focus is placed on integrative omics tools, including genome mining, Global Natural Products Social Molecular Networking (GNPS), and multi-omics strategies that streamline isolation, structural elucidation, and bioactivity-guided research. Case studies from the Red Sea and African waters further illustrate the critical role of marine natural products in advancing regional and global biomedical innovation.

Keywords: *marine natural products; omics technologies; drug discovery; metabolomics; genome mining; bioactive metabolites; biomedical innovation*

Introduction

Natural products remain among the most prolific sources of therapeutic agents, with nearly half of all approved drugs originating directly or indirectly from natural sources such as plants, microbes, and marine

organisms (Banday et al., 2024; Newman & Cragg, 2020). Marine ecosystems, in particular, are now recognised as exceptional reservoirs of structurally unique and biologically potent metabolites (Carroll et al., 2022; Jayawardena et al., 2025; Tan, 2023). Occupying over 70% of the Earth's surface, the oceans host diverse organisms that have evolved under extreme conditions of salinity, pressure, and ecological competition. These selective pressures drive the production of distinctive chemical defenses in sponges, corals, tunicates, algae, and marine microorganisms, yielding metabolites with scaffolds and pharmacological features rarely observed in terrestrial species (Bharathi & Lee, 2024; Guryanova & Ovchinnikova, 2025; Leal et al., 2012; Tan, 2023).

Several marine-derived pharmaceuticals, including trabectedin, brentuximab vedotin, and plocabulin, have reached clinical application, illustrating the translational promise of this chemical space (Atanasov et al., 2021; Cappello & Nieri, 2021; De Sanctis et al., 2022; Mayer et al., 2010). Despite this success, research on marine natural products (MNPs) continues to face challenges related to low natural abundance, sustainability concerns, and structural complexity (Banday et al., 2024; Gaudêncio et al., 2023; Gaudêncio & Pereira, 2015; Shen et al., 2022). Moreover, conventional isolation approaches are labor-intensive and frequently lead to the rediscovery of known metabolites.

The advent of omics technologies—including genomics, transcriptomics, proteomics, and metabolomics—has transformed this landscape (Aborode et al., 2022; Baysoy et al., 2023; Mudadla et al., 2024; Sahana et al., 2025; Satrio et al., 2024). These tools provide insights into biosynthetic gene clusters, facilitate dereplication of known metabolites, and reveal cryptic compounds that remain silent under standard culture conditions (Gaudêncio et al., 2023; Hur et al., 2023; Sheikh et al., 2025; van Der Hooft et al., 2020). Integrative multi-omics strategies, coupled with computational approaches such as molecular networking and genome mining, are now linking genes to molecules, greatly accelerating compound discovery (Albarano et al., 2020; Joshi et al., 2024; Liu & Zhang, 2024; Sadybekov & Katritch, 2023; Wang et al., 2016).

Recent work demonstrates how these methodologies enable high-throughput dereplication, pathway elucidation, and prioritisation of bioactive metabolites (Dasí-Delgado et al., 2025; Gaudêncio et al., 2023; Kaur et al., 2025; Liao et al., 2025). Incorporating artificial intelligence (AI) and machine learning (ML) into omics workflows further enhances predictive capacity, improving both metabolite annotation and drug-target interaction modelling (Ali, 2023; Jamalabadi, 2025; Kim et al., 2021;

Kumar & Sadashiva, 2025). Collectively, these advances are expanding the known chemical and pharmacological space while streamlining the translation of marine metabolites into biomedical applications.

This review summarizes current progress in marine natural product research within the omics era, focusing on integrative strategies that facilitate isolation, structural elucidation, and drug discovery. Emphasis is placed on anticancer, antimicrobial, antiviral, and anti-inflammatory applications, with case studies from the Red Sea and African coastal waters highlighting the promise of underexplored regions. By synthesizing these developments, we underline the central role of omics-driven research in unlocking the biomedical potential of marine natural products and advancing translational innovation.

Marine Natural Products – Historical and Biomedical Significance

Marine ecosystems rank among the most chemically diverse environments on Earth. The structural originality and potent bioactivities of marine natural products (MNPs) have drawn extensive scientific and pharmaceutical attention for more than half a century. Since the discovery of the first marine-derived metabolite, spongothymidine, from a Caribbean sponge in the 1950s, marine organisms have continued to yield unique molecular scaffolds that have inspired several successful drugs and clinical leads (Holland, 2022; Mayer et al., 2010; Newman & Cragg, 2020; Raymond & Rakotondraibe, 2025).

Historical contributions to drug discovery

Numerous marine-derived compounds or their synthetic analogues have achieved clinical approval, underscoring the translational potential of this field:

- **Cytarabine (Ara-C)** – derived from spongothymidine and approved in 1969 for leukemia and lymphoma.
- **Trabectedin (Yondelis®)** – isolated from the tunicate Ecteinascidia turbinata, used in the treatment of soft tissue sarcoma and ovarian cancer.
- **Ziconotide (Prialt®)** – a synthetic analogue of a cone snail peptide, serving as a potent analgesic for severe chronic pain.
- **Brentuximab vedotin (Adcetris®)** – an antibody–drug conjugate employing a dolastatin-10 derivative as a cytotoxic payload for Hodgkin's lymphoma.

- **Eribulin mesylate (Halaven®)** – a synthetic analogue of halichondrin B from the sponge Halichondria okadai, approved for metastatic breast cancer.

These examples demonstrate that marine metabolites often provide pharmacophores beyond the reach of traditional synthetic chemistry (Atanasov et al., 2021; Carroll et al., 2022; Servillera et al., 2025; Zhao et al., 2023).

In addition to these approved drugs (Table 1), several marine-derived candidates are under clinical investigation across oncology, pain management, and antiviral research. Collectively, they highlight the continuing evolution of marine natural products from discovery to clinical application (Banday et al., 2024; Carroll et al., 2022; Newman & Cragg, 2020).

Drug (Year Approved)	Natural Source	Therapeutic Class	Clinical Indication	Mechanism of Action	Reference
Cytarabine (Ara-C, 1969)	*Cryptotethya crypta* (sponge, precursor spongothymidine)	Antimetabolite (nucleoside analogue)	Acute myeloid leukemia, lymphoma	Inhibits DNA polymerase, blocks DNA synthesis	(Mayer et al., 2010)
Vidarabine (Ara-A, 1976)	*Cryptotethya crypta*	Antiviral (nucleoside analogue)	Herpes simplex, varicella-zoster	Inhibits viral DNA polymerase	(Mayer et al., 2010)
Trabectedin (Yondelis®, 2007 EU / 2015 US)	*Ecteinascidia turbinata* (tunicate)	Alkaloid	Soft tissue sarcoma, ovarian cancer	Binds DNA minor groove, disrupts transcription factors	(Newman & Cragg, 2020)
Eribulin mesylate (Halaven®, 2010)	Synthetic analogue of *Halichondrin B* (sponge)	Microtubule dynamics inhibitor	Metastatic breast cancer, liposarcoma	Inhibits microtubule growth, induces apoptosis	(Cragg & Pezzuto, 2015)
Brentuximab vedotin (Adcetris®, 2011)	Synthetic derivative of *Dolastatin 10* (sea hare *Dolabella auricularia*)	Antibody–drug conjugate (ADC)	Hodgkin's lymphoma, anaplastic large cell lymphoma	Delivers auristatin (MMAE) to CD30+ cells	(Whitesell & Minton, 1987)
Plitidepsin (Aplidin®, 2018 EU)	*Aplidium albicans* (tunicate)	Cyclic depsipeptide	Multiple myeloma	Induces oxidative stress, inhibits eEF1A2	(Seyed & Ayesha, 2021)
Polatuzumab vedotin (Polivy®, 2019)	ADC with MMAE (dolastatin derivative)	ADC	Diffuse large B-cell lymphoma	Delivers MMAE to CD79b+ B-cells	Beck et al., 2017
Enfortumab vedotin (Padcev®, 2019)	ADC with MMAE	ADC	Urothelial carcinoma	Targets Nectin-4, delivers MMAE	(Beck et al., 2017)
Belantamab mafodotin (Blenrep®, 2020 EU/US)	ADC with MMAF (dolastatin derivative)	ADC	Relapsed/refractory multiple myeloma	Targets BCMA, induces apoptosis	(Lonial et al., 2020)
Tisotumab vedotin (Tivdak®, 2021)	ADC with MMAE	ADC	Cervical cancer	Targets tissue factor, delivers MMAE	(Bogani et al., 2023)

Table 1. Selected approved marine-derived drugs and their clinical indications

Biomedical relevance of marine natural products

Marine-derived metabolites are characterised by several unique features that distinguish them from terrestrial counterparts:

- Exceptional structural diversity: they encompass polyketides, peptides, terpenoids, alkaloids, and hybrid scaffolds that are seldom encountered in land-based organisms (Carroll et al., 2022; Leal et al., 2012; Martínez et al., 2025).
- High biological potency: many exhibit activity at nanomolar or picomolar concentrations, reflecting remarkable pharmacological strength (Efimova & Ostroumova, 2023; Newman & Cragg, 2020).
- Broad therapeutic potential: marine compounds display anticancer, antiviral (including activity against HIV, herpes, and SARS-CoV-2), antibacterial (notably against resistant strains such as MRSA), anti-inflammatory, immunomodulatory, and neuroprotective effects (Atanasov et al., 2021; El-Saadony et al., 2025; Mayer et al., 2010).

Beyond the clinically approved drugs, numerous marine metabolites are progressing through preclinical and clinical development (Banday et al., 2024; Carroll et al., 2022). Marine-inspired pharmacophores also continue to influence rational drug design and synthetic optimisation in medicinal chemistry (Fernández et al., 2024; Newman & Cragg, 2020).

Significant discoveries have emerged from African and Red Sea ecosystems, which remain underrepresented in global drug discovery pipelines (Abd El Hafez et al., 2025; El-Seedi et al., 2025). Soft corals such as Sarcophyton trocheliophorum, Litophyton arboreum, Sinularia polydactyla, and Nephthea spp. have yielded cytotoxic sesquiterpenoids, diterpenes, and steroidal derivatives active against breast, liver, and leukemia cell lines (Eissa et al., 2025; M. Han et al., 2024; Yan et al., 2023; Yang et al., 2022). Likewise, Red Sea sponges including Stylissa carteri and Haliclona spp. have produced peptides and alkaloids with notable antimicrobial and anticancer potential (Rahman et al., 2024; Strashnova et al., 2024). Despite these promising findings, most compounds remain at early pharmacological stages, underscoring the need for omics-driven approaches to prioritize leads and elucidate mechanisms of action.

Omics Technologies in Marine Natural Product Research

Over the past decade, omics-based technologies have transformed strategies for discovering marine natural products (MNPs). Genomics, transcriptomics, proteomics, and metabolomics enable rapid, high-throughput assessment of biosynthetic potential, regulatory mechanisms, and chemical diversity, facilitating targeted discovery, dereplication, and identification of otherwise cryptic metabolites. Integrative omics workflows that merge bioinformatics, mass spectrometry, and

experimental biology now directly link genes to molecules, accelerating the identification and development of promising bioactive leads (Atanasov et al., 2021; Lauritano et al., 2019; Roychowdhury et al., 2023; Vitorino, 2024; Q. Zhou et al., 2021). An overview of the integrated omics pipeline employed in modern marine natural product discovery is presented in Figure 1.

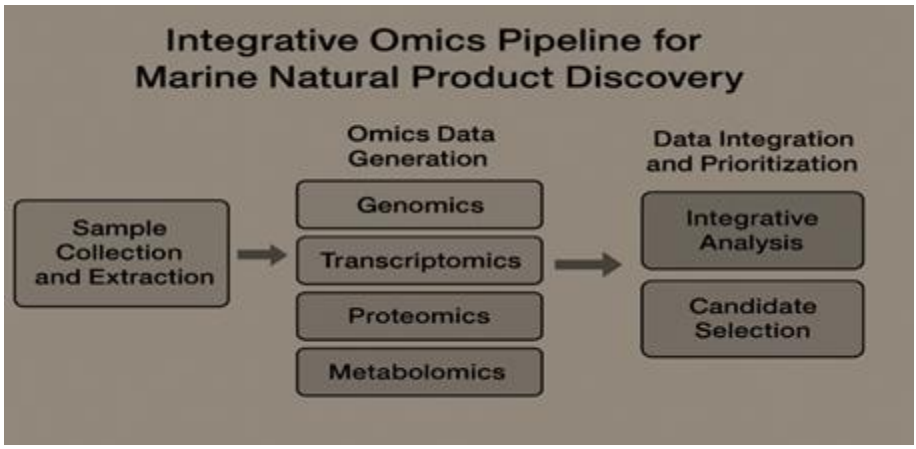

Figure 1. Integrative Omics Pipeline for Marine Natural Product Discovery

Metabolomics and Global Natural Products Social Molecular Networking (GNPS)

Untargeted LC–MS/MS metabolomics generates chemical fingerprints of extracts and fractions. Global Natural Products Social Molecular Networking (GNPS) and Feature-Based Molecular Networking (FBMN) visualise MS/MS datasets as networks of related spectra, facilitating dereplication, annotation transfer, and discovery of analogue series or novel scaffolds. FBMN further incorporates chromatographic data, improving quantitation and distinguishing coeluting isomers (Gaudêncio et al., 2023; Leao et al., 2021; Nothias et al., 2020; Zhang et al., 2023).

Applications:

- **Dereplication**: rapidly identify known compounds to prioritize novel nodes.
- **Analogue discovery**: detect clusters of related molecules indicating natural-product families or modification series.
- **Linking chemistry to biology**: integrate MS-based features with bioactivity data to prioritize active nodes (Schmid et al., 2021; Selegato et al., 2023).

Best practices:

- Acquire high-quality MS/MS (DDA or DIA) and apply robust pre-processing (e.g., MZmine, MS-DIAL).
- Deposit spectra in public libraries and use spectral matching plus in silico tools (SIRIUS, MS2LDA) for structural hypotheses (Leao et al., 2021; Russo et al., 2024; Schmid et al., 2021).

Pilot studies from the Red Sea and African coasts illustrate the power of omics-guided workflows in underexplored ecosystems (Puntin et al., 2022; Tenchov & Zhou, 2025). LC–MS/MS metabolomics combined with GNPS has revealed diverse terpene- and peptide-rich clusters from Red Sea soft corals (*Litophyton*, *Sarcophyton*) and sponge-associated microbiomes, enabling rapid dereplication and uncovering potentially novel scaffolds (Churakova, 2020; Farag et al., 2024; Hegazi et al., 2022). Concurrently, genome-mining of African marine actinomycetes and sponge-associated bacteria has identified NRPS and PKS BGCs with uncharacterized chemistry, highlighting the untapped potential of these regions (Hemmerling & Piel, 2022; Lotti, 2024; Mhlongo, 2021). Together, these studies demonstrate that integrating metabolomics, genome mining, and AI-assisted annotation can accelerate natural product discovery in Africa and the Red Sea (Ali et al., 2024; Liao et al., 2025).

Integrative multi-omics and computational linking

Combining genomics, transcriptomics/proteomics, and MS-based metabolomics enables gene-to-molecule mapping. Methods include correlation-based linking, genome-enabled dereplication, and in silico prediction (e.g., PRISM, NP. searcher). Metabologenomics, linking BGCs with GNPS networks, has guided heterologous production and metabolite assignment (Cano-Prieto et al., 2024; Louwen et al., 2023; Nothias et al., 2020; Skinnider et al., 2020).

Computational tools, databases and pipelines

- **antiSMASH / antiSMASH database** (BGC detection and annotation) (K. Blin et al., 2023; Kai Blin et al., 2023; Blin et al., 2025).
- **PRISM** (structure prediction from genomic data) (Shaikovski et al., 2024; Skinnider et al., 2020).
- **GNPS / FBMN** (MS/MS molecular networking and community spectral libraries) (David et al., 2025; Nothias et al., 2020).
- **SIRIUS, MS2LDA, MZmine, MS-DIAL** (MS data processing and in-silico annotation) (David et al., 2025; Leao et al., 2021; Rutz et al., 2025).

- **Public databases**: MIBiG (characterized BGCs), antiSMASH DB, GNPS libraries, NPAtlas (Kai Blin et al., 2023; Wackett, 2018; Zhang et al., 2024; Zhu et al., 2025).

Table 2. Representative omics-driven approaches in marine natural product discovery

Omics approach	Tool/Platform	Marine source organism	Highlighted outcome	Reference
Genome mining	antiSMASH, PRISM	*Salinispora tropica* (marine actinomycete)	Identification of salinosporamide biosynthetic gene cluster; guided discovery of proteasome inhibitor.	(Udwary et al., 2007)
Metabolomics	GNPS molecular networking	Marine cyanobacteria and sponges	Discovery and dereplication of novel metabolites; accelerated prioritisation of bioactive compounds	(Kleigrewe et al., 2015)
Transcriptomics	RNA-Seq + co-expression analysis	Sponge *Theonella swinhoei* (with symbionts)	Elucidation of symbiont role in biosynthesis of polytheonamides.	(Wilson et al., 2014)
Multi-omics (genome + metabolome)	Integrated omics pipeline (genome mining + metabolomics)	*Salinispora arenicola*	Discovery of novel rifamycin derivatives via biosynthetic–metabolite correlation.	(Duncan et al., 2015)
Proteomics	MS-based proteomics	Cyanobacterium *Moorea producens*	Characterisation of enzyme clusters linked to lyngbyatoxin biosynthesis.	(Leao et al., 2017)

Integration pipelines often consist of:

Typical omics integration pipelines involve:

1. Sequence assembly → BGC detection (antiSMASH/PRISM).
2. LC–MS/MS acquisition → preprocessing (MZmine/MS-DIAL) → FBMN (GNPS).
3. Correlation and in silico linking (Metabologenomics) to propose gene-to-molecule relationships (Harper et al., 2024; Selegato et al., 2023; Skinnider et al., 2020).

Representative applications are summarised in Table 2, while Table 3 lists selected marine-derived compounds in advanced preclinical or clinical stages. Clinical development data were cross-checked via ClinicalTrials.gov, recent pharmaceutical reports (2023–2025), and peer-reviewed reviews. Key updates include.

- **Plitidepsin (Aplidin®):** Advanced clinical evaluation for multiple myeloma; investigator-led studies explore antiviral and anticancer potential (Papapanou et al., 2021).

- **Plocabulin (PM060184):** Phase I/early Phase II trials, including combinations with gemcitabine for advanced solid tumours (Mohammad H Ghalib et al., 2024).
- **PM00104 (Zalypsis®):** Phase I/II trials ongoing for Ewing sarcoma, urothelial carcinoma, and other malignancies (Qin Zhou et al., 2021).
- **Marizomib (Salinosporamide A / NPI-0052):** Phase I trials continue for glioma, multiple myeloma, and CNS tumours (Kusaczuk et al., 2025b).
- **Tetrodotoxin (TTX):** Phase II/III studies for chemotherapy-induced neuropathic pain and cancer-associated pain, with updates through 2023–2024 (Antoniazzi et al., 2024; Szallasi, 2024; Zhou et al., 2025).

These concise updates provide an evidence-based view of ongoing marine-derived clinical development.

Table 3. Selected marine-derived candidates in clinical development (2023–2025)

Candidate (trade name / code)	Source / origin	Clinical phase (latest public record)	Indication(s)	Developer / Sponsor	Key notes & sources
Plitidepsin (Aplidin®)	Cyclic depsipeptide from tunicate *Aplidium albicans*	Phase III / advanced trials (2023–2024); regulatory activity 2024–2025	Multiple myeloma; investigated for COVID-19 (hospitalised moderate cases) and other malignancies	PharmaMar	Phase III trial reports and company updates; trial data for COVID-19 and oncology trials (Landete et al., 2024).
Plocabulin (PM060184; Plo)	Microtubule inhibitor originally from marine sponge (Lithoplocamia spp.)	Phase I → Phase II activities (ongoing studies reported 2022–2024)	Advanced/solid tumours (various), combinations with gemcitabine explored	PharmaMar / Pharma collaborators	First-in-human Phase I published; recent Phase I combination trial (plocabulin + gemcitabine) and ongoing development (Elez et al., 2019; M. H. Ghalib et al., 2024).
PM00104 (Zalypsis®)	Marine-derived alkylating agent (synthetic derivative inspired by marine natural product)	Phase II (historical and ongoing investigator trials)	Ewing sarcoma, urothelial carcinoma, multiple myeloma, endometrial/cervical cancer (various trials)	PharmaMar / ZeClinics (investigators)	Multiple Phase I/II studies and PK trials reported; ongoing investigator-led Phase II reports (Martin et al., 2013; Petek & Jones, 2014).
Marizomib (NPI-0052; Salinosporamide A)	Proteasome inhibitor from marine actinomycete *Salinispora tropica*	Phase I / early phase trials (ongoing/repurposing studies through 2024–2025)	Multiple myeloma, glioma (brain tumours), other malignancies	Nereus Pharmaceuticals / Salinosporamide developers	Evaluated in multiple Phase I trials; continued clinical investigation for CNS tumours and hematologic malignancies (Kusaczuk et al., 2025a; Potts et al., 2011).
Tetrodotoxin (Halneuron® / TTX)	Marine neurotoxin (puffer fish or purified TTX)	Phase II → Phase III (neuropathic / cancer pain: ongoing trials 2022–2025)	Chemotherapy-induced neuropathic pain, cancer pain, other neuropathic pain conditions	WEX Pharmaceuticals / Dogwood (development partners)	Randomised Phase II/2B and Phase 2b/3 trials for chemotherapy-induced neuropathic pain and cancer pain; active development and presentations 2023–2024.

Selected case studies and examples

1. **Molecular networking reveals analogue families**: FBMN enables discovery of analogue series in marine extracts, prioritizing novel nodes for isolation and structural characterisation (Bracegirdle, 2023; Leao et al., 2021; Nothias et al., 2020).
2. **Genome mining in marine fungi and bacteria**: PKS/NRPS clusters in marine fungi and actinomycetes guide discovery of new polyketides and peptides, illustrating BGC-led prioritisation (C. Han et al., 2024; Ibrahim et al., 2025).
3. **Metabologenomics linking**: Integration of antiSMASH/PRISM with GNPS links genomic loci to MS clusters, enabling heterologous expression and pathway validation (Nothias et al., 2020; Sheikh et al., 2025; Skinnider et al., 2020).

Despite global expansion, studies from Africa and the Red Sea remain underrepresented. Pilot LC–MS/MS metabolomics and molecular networking on Red Sea soft corals demonstrate potential for novel metabolites, but comprehensive genome mining is still limited. Expanding omics resources in African marine ecosystems could accelerate bioactive compound discovery.

Integrative Approaches for Drug Discovery

The structural complexity of marine natural products demands workflows combining classical isolation with omics and computational tools, improving discovery efficiency (Atanasov et al., 2021; Newman & Cragg, 2020; Sadybekov & Katritch, 2023). For example, combining metabolomics with bioassay-guided screening links GNPS networks with cytotoxicity in sponge-associated bacteria, prioritizing unique clusters for structural elucidation (Carroll et al., 2024; Leao et al., 2017; Schmid et al., 2021), particularly in underexplored African taxa (Ibrahim et al., 2025).

Bioactivity-Guided Fractionation and Dereplication

Bioactivity-guided fractionation remains powerful for isolating active compounds but can be redundant. High-resolution LC–MS/MS dereplication using GNPS or MarinLit enables rapid recognition of known metabolites and prioritisation of novel entities (Das & Shafi, 2023; Leao et al., 2021; Li et al., 2024; Mayer et al., 2010; Nothias et al., 2020; Sarkar et al., 2025).

Synergy of Omics and Bioassays

Modern workflows integrate omics with high-throughput screening to link metabolic features with bioactivity, facilitating biomarker identification (Selegato et al., 2023). Transcriptomics and proteomics help elucidate molecular targets of marine compounds, bridging chemistry and pharmacology (Atanasov et al., 2021; Moutinho Cabral et al., 2024; Q. Zhou et al., 2021).

Computational Approaches for Drug-Target Interaction

Docking, molecular dynamics, and pharmacophore modelling predict drug–target interactions. AI-driven network pharmacology integrates omics with structural data to map polypharmacology, enabling drug repositioning (Atanasov et al., 2021; Bhatia et al., 2024; Newman & Cragg, 2020; Shehab et al., 2024; van Der Hooft et al., 2020). Deep generative models predict NRPS/PKS products before isolation (Carretero Molina, 2024; Q. Zhou et al., 2021).

Challenges, Limitations, and Future Perspectives

Supply and Sustainability: Trace metabolite production limits large-scale isolation. Overharvesting raises ecological concerns, necessitating aquaculture, synthesis, or sustainable collection (Bhadange et al., 2024; Mayer et al., 2010; Newman & Cragg, 2020).

Redundancy and Dereplication: Known compounds are frequently re-isolated. Spectral limitations and structural complexity make integration of AI-enhanced dereplication essential (Gaudêncio et al., 2023; Leao et al., 2021; Nothias et al., 2020; Sabol, 2025; Selegato et al., 2023; van Der Hooft et al., 2020).

Technical Constraints: Low MS ionization, overlapping NMR signals, and limited proteomic/transcriptomic sensitivity challenge minor metabolite detection (Chaudhary et al., 2021; Ferreira et al., 2024; Skinnider et al., 2020).

Interdisciplinary Needs: Effective MNP research requires collaboration across chemistry, biology, pharmacology, computational science, and ecology. Consortia and academia-industry partnerships are vital (Atanasov et al., 2021; Newman & Cragg, 2020; Seibert & Friedrich, 2024).

Ethical and Legal Considerations: Marine bioprospecting must comply with Access and Benefit Sharing (ABS) under the Nagoya Protocol. Key concerns include sovereignty, equitable benefit-sharing, responsible collection, and handling of digital sequence information (DSI), especially in African and Red Sea regions. Strengthening national

policies, transparent MTAs, and local capacity building are crucial for ethical, sustainable research.

Future Perspectives

- **Synthetic biology & genome mining:** Engineer pathways to enhance yields and produce analogues (Skinnider et al., 2020; Wang et al., 2025; Q. Zhou et al., 2021).
- **AI & ML:** Streamline dereplication, scaffold prediction, and drug-target validation (Selegato et al., 2023; van Der Hooft et al., 2020).
- **Microbiome exploration:** Investigate sponge and coral symbionts for untapped secondary metabolites (Couceiro et al., 2025; Doering et al., 2021; Leao et al., 2021).
- **Sustainable production:** Green chemistry and aquaculture reduce environmental impact (Atanasov et al., 2021; Shetranjiwalla & Ononiwu, 2025).
- **Regional development:** Expand omics infrastructure in Africa and Red Sea ecosystems, integrating genome mining, molecular networking, and high-resolution analytics to convert local biodiversity into global biomedical innovations, while ensuring ABS compliance.

Conclusions

Marine natural products (MNPs) provide structurally diverse and pharmacologically potent scaffolds, exemplified by cytarabine, trabectedin, and eribulin. Omics technologies, AI, and computational tools have transformed discovery pipelines, linking bioactivity-guided isolation with genomics, proteomics, and metabolomics.

Challenges remain in supply, technical limitations, and ecological sustainability, requiring synthetic biology, aquaculture, microbiome studies, and interdisciplinary collaboration.

Future efforts should focus on underexplored regions such as Africa and the Red Sea, developing omics databases, promoting collaboration, and ensuring sustainable collection. With these strategies, MNPs will continue to contribute substantially to drug discovery, offering solutions to antimicrobial resistance, cancer, and emerging infectious diseases.

References:

Abd El Hafez, M. S., Maiyza, A. I., Hassan, H. A., Osama, S., Seadawy, M. G., El Demellawy, M. A., & Ghareeb, D. A. (2025). Analytical and machine learning approaches identify a sea star steroid with promising activity for COVID-19 therapeutic development. *Scientific Reports*, *15*(1), 35013.

Aborode, A. T., Awuah, W. A., Mikhailova, T., Abdul-Rahman, T., Pavlock, S., Kundu, M., Yarlagadda, R., Pustake, M., Correia, I. F. d. S., & Mehmood, Q. (2022). OMICs technologies for natural compounds-based drug development. *Current Topics in Medicinal Chemistry*, *22*(21), 1751-1765.

Albarano, L., Esposito, R., Ruocco, N., & Costantini, M. (2020). Genome mining as new challenge in natural products discovery. *Marine Drugs*, *18*(4), 199.

Ali, H. (2023). Artificial intelligence in multi-omics data integration: Advancing precision medicine, biomarker discovery and genomic-driven disease interventions. *Int J Sci Res Arch*, *8*(1), 1012-1030.

Ali, M., Shabbir, K., Ali, S., Mohsin, M., Kumar, A., Aziz, M., Zubair, M., & Sultan, H. M. (2024). A new era of discovery: how artificial intelligence has revolutionized the biotechnology. *Nepal Journal of Biotechnology*, *12*(1), 1-11.

Antoniazzi, C. T., Kudsi, S. Q., da Silva, B., Pereira, L. G., Frare, J. M., & Trevisan, G. (2024). New Targets for Cancer Pain Relief. In. Springer.

Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., Orhan, I. E., Banach, M., Rollinger, J. M., Barreca, D., Weckwerth, W., Bauer, R., Bayer, E. A., Majeed, M., Bishayee, A., Bochkov, V., Bonn, G. K., Braidy, N., Bucar, F., Cifuentes, A., D'Onofrio, G., Bodkin, M., . . . the International Natural Product Sciences, T. (2021). Natural products in drug discovery: advances and opportunities. *Nature Reviews Drug Discovery*, *20*(3), 200-216. https://doi.org/10.1038/s41573-020-00114-z

Banday, A. H., ul Azha, N., Farooq, R., Sheikh, S. A., Ganie, M. A., Parray, M. N., Mushtaq, H., Hameed, I., & Lone, M. A. (2024). Exploring the potential of marine natural products in drug development: A comprehensive review. *Phytochemistry Letters*, *59*, 124-135.

Baysoy, A., Bai, Z., Satija, R., & Fan, R. (2023). The technological landscape and applications of single-cell multi-omics. *Nature Reviews Molecular Cell Biology*, *24*(10), 695-713.

Beck, A., Goetsch, L., Dumontet, C., & Corvaïa, N. (2017). Strategies and challenges for the next generation of antibody–drug conjugates. *Nature*

Reviews Drug Discovery, *16*(5), 315-337. https://doi.org/10.1038/nrd.2016.268

Bhadange, Y. A., Carpenter, J., & Saharan, V. K. (2024). A comprehensive review on advanced extraction techniques for retrieving bioactive components from natural sources. *ACS omega*, *9*(29), 31274-31297.

Bharathi, D., & Lee, J. (2024). Recent advances in marine-derived compounds as potent antibacterial and antifungal agents: A comprehensive review. *Marine Drugs*, *22*(8), 348.

Bhatia, N., Khan, M. M. U., & Arora, S. (2024). The role of artificial intelligence in revolutionizing pharmacological research. *Current Pharmacology Reports*, *10*(6), 323-329.

Blin, K., Shaw, S., Augustijn, H. E., Reitz, Z. L., Biermann, F., Alanjary, M., Fetter, A., Terlouw, B. R., Metcalf, W. W., Helfrich, E. J. N., van Wezel, G. P., Medema, M. H., & Weber, T. (2023). antiSMASH 7.0: new and improved predictions for detection, regulation, chemical structures and visualisation. *Nucleic Acids Research*, *51*(W1), W46-w50. https://doi.org/10.1093/nar/gkad344

Blin, K., Shaw, S., Medema, M. H., & Weber, T. (2023). The antiSMASH database version 4: additional genomes and BGCs, new sequence-based searches and more. *Nucleic Acids Research*, *52*(D1), D586-D589. https://doi.org/10.1093/nar/gkad984

Blin, K., Shaw, S., Vader, L., Szenei, J., Reitz, Z. L., Augustijn, H. E., Cediel-Becerra, J. D., de Crécy-Lagard, V., Koetsier, R. A., & Williams, S. E. (2025). antiSMASH 8.0: extended gene cluster detection capabilities and analyses of chemistry, enzymology, and regulation<? mode pagerangestyle?>. *Nucleic Acids Research*, gkaf334.

Bogani, G., Coleman, R. L., Vergote, I., Raspagliesi, F., Lorusso, D., & Monk, B. J. (2023). Tisotumab vedotin in recurrent or metastatic cervical cancer. *Current problems in cancer*, *47*(3), 100952.

Bracegirdle, J. (2023). *Chemical Investigations of Pacific Marine Organisms* Open Access Te Herenga Waka-Victoria University of Wellington].

Cano-Prieto, C., Undabarrena, A., de Carvalho, A. C., Keasling, J. D., & Cruz-Morales, P. (2024). Triumphs and challenges of natural product discovery in the postgenomic era. *Annual Review of Biochemistry*, *93*.

Cappello, E., & Nieri, P. (2021). From life in the sea to the clinic: The marine drugs approved and under clinical trial. *Life*, *11*(12), 1390.

Carretero Molina, D. (2024). *Expanding the chemical space of microbial specialized metabolites: Structure elucidation and biosynthesis of novel bioactive natural products from actinomycetes* Universidad de Granada].

Carroll, A. R., Copp, B. R., Davis, R. A., Keyzers, R. A., & Prinsep, M. R. (2022). Marine natural products. *Natural product reports*, *39*(6), 1122-1171.

Carroll, A. R., Copp, B. R., Grkovic, T., Keyzers, R. A., & Prinsep, M. R. (2024). Marine natural products. *Natural Product Reports*, *41*(2), 162-207.

Chaudhary, S., Chaudhary, P., & Patel, S. (2021). Genomics, transcriptomics, proteomics and metabolomics approaches. In *Fenugreek: Biology and applications* (pp. 355-373). Springer.

Churakova, Y. (2020). *Metabolomic and metagenomic study of Lake Baikal diseased sponges* UiT Norges arktiske universitet].

Couceiro, J. F., Costa, R., & Keller-Costa, T. (2025). Beyond Restoration: Coral Microbiome Biotechnology. *Coral Reef Microbiome*, 215-234.

Cragg, G. M., & Pezzuto, J. M. (2015). Natural Products as a Vital Source for the Discovery of Cancer Chemotherapeutic and Chemopreventive Agents. *Medical Principles and Practice*, *25*(Suppl. 2), 41-59. https://doi.org/10.1159/000443404

Das, D., & Shafi, S. (2023). Bioactivity-guided fractionation and identification of bioactive molecules: A basic method in drug discovery. In *Drugs and a Methodological Compendium: From bench to bedside* (pp. 41-78). Springer.

Dasí-Delgado, P., Andreu, C., & del Olmo, M. l. (2025). Strategies Used for the Discovery of New Microbial Metabolites with Antibiotic Activity. *Molecules*, *30*(13), 2868.

David, P. A., Norazhar, A. I., & Che Zain, M. S. (2025). Integrating LC-MS/MS and Molecular Networking for Advance Analysis and Comprehensive Flavonoids Annotation. *Journal of Separation Science*, *48*(7), e70230.

De Sanctis, R., Jacobs, F., Benvenuti, C., Gaudio, M., Franceschini, R., Tancredi, R., Pedrazzoli, P., Santoro, A., & Zambelli, A. (2022). From seaside to bedside: Current evidence and future perspectives in the treatment of breast cancer using marine compounds. *Frontiers in pharmacology*, *13*, 909566.

Doering, T., Wall, M., Putchim, L., Rattanawongwan, T., Schroeder, R., Hentschel, U., & Roik, A. (2021). Towards enhancing coral heat tolerance: a "microbiome transplantation" treatment using inoculations of homogenized coral tissues. *Microbiome*, *9*(1), 102.

Duncan, K. R., Crüsemann, M., Lechner, A., Sarkar, A., Li, J., Ziemert, N., Wang, M., Bandeira, N., Moore, B. S., & Dorrestein, P. C. (2015). Molecular networking and pattern-based genome mining improves discovery of biosynthetic gene clusters and their products from Salinispora species. *Chemistry & biology*, *22*(4), 460-471.

Efimova, S. S., & Ostroumova, O. S. (2023). Modulation of the Dipole Potential of Model Lipid Membranes with Phytochemicals: Molecular Mechanisms, Structure–Activity Relationships, and Implications in Reconstituted Ion Channels. *Membranes*, *13*(4), 453.

Eissa, A. H., Aboseada, H. A., & Ayyad, S. E. N. (2025). New Bioactive Eudesmane-type Sesquiterpenoids From the Red Sea Soft Coral Nephthea sp. *Chemistry & Biodiversity*, e02473.

El-Saadony, M. T., Saad, A. M., Mohammed, D. M., Korma, S. A., Alshahrani, M. Y., Ahmed, A. E., Ibrahim, E. H., Salem, H. M., Alkafaas, S. S., & Saif, A. M. (2025). Medicinal plants: bioactive compounds, biological activities, combating multidrug-resistant microorganisms, and human health benefits-a comprehensive review. *Frontiers in immunology*, *16*, 1491777.

El-Seedi, H. R., Refaey, M. S., Elias, N., El-Mallah, M. F., Albaqami, F. M., Dergaa, I., Du, M., Salem, M. F., Tahir, H. E., & Dagliaa, M. (2025). Marine natural products as a source of novel anticancer drugs: an updated review (2019–2023). *Natural Products and Bioprospecting*, *15*(1), 13.

Elez, E., Gomez-Roca, C., Soto Matos-Pita, A., Argiles, G., Valentin, T., Coronado, C., Iglesias, J., Macarulla, T., Betrian, S., Fudio, S., Zaragoza, K., Tabernero, J., & Delord, J. P. (2019). First-in-human phase I study of the microtubule inhibitor plocabulin in patients with advanced solid tumors. *Invest New Drugs*, *37*(4), 674-683. https://doi.org/10.1007/s10637-018-0674-x

Farag, M. A., El-Kammar, H. A., Abdelghany, S., & El-Akad, R. H. (2024). Seasonal and taxa impact on edible sea cucumber's metabolome and in relation to its cytotoxicity as analyzed via UHPLC/HR-MS/MS-based molecular networking and chemometrics. *Food Frontiers*, *5*(2), 584-606.

Fernández, S., Arnáiz, V., Rufo, D., & Arroyo, Y. (2024). Current status of indole-derived marine natural products: synthetic approaches and therapeutic applications. *Marine Drugs*, *22*(3), 126.

Ferreira, C. R., de Lima Gomes, P. C. F., Robison, K. M., Cooper, B. R., & Shannahan, J. H. (2024). Implementation of multiomic mass spectrometry approaches for the evaluation of human health following environmental exposure. *Molecular Omics*, *20*(5), 296-321.

Gaudêncio, S. P., Bayram, E., Lukić Bilela, L., Cueto, M., Díaz-Marrero, A. R., Haznedaroglu, B. Z., Jimenez, C., Mandalakis, M., Pereira, F., & Reyes, F. (2023). Advanced methods for natural products discovery: bioactivity screening, dereplication, metabolomics profiling, genomic sequencing, databases and informatic tools, and structure elucidation. *Marine Drugs*, *21*(5), 308.

Gaudêncio, S. P., & Pereira, F. (2015). Dereplication: racing to speed up the natural products discovery process [10.1039/C4NP00134F]. *Natural Product Reports*, *32*(6), 779-810. https://doi.org/10.1039/C4NP00134F

Ghalib, M. H., Pulla, M. P., De Miguel Luken, M. J., de Juan, V. C., Chaudhary, I., Hammami, M. B., Vikash, S., Maitra, R., Martinez, S., &

Kahatt, C. (2024). A phase I safety and efficacy clinical trial of plocabulin and gemcitabine in patients with advanced solid tumors. *Investigational New Drugs*, *42*(5), 481-491.

Ghalib, M. H., Pulla, M. P., De Miguel Luken, M. J., de Juan, V. C., Chaudhary, I., Hammami, M. B., Vikash, S., Maitra, R., Martinez, S., Kahatt, C., Extremera, S., Fudio, S., & Goel, S. (2024). A phase I safety and efficacy clinical trial of plocabulin and gemcitabine in patients with advanced solid tumors. *Invest New Drugs*, *42*(5), 481-491. https://doi.org/10.1007/s10637-024-01458-8

Guryanova, S. V., & Ovchinnikova, T. V. (2025). Multifaceted Marine Peptides and Their Therapeutic Potential. *Marine Drugs*, *23*(7), 288.

Han, C., Song, A., He, Y., Yang, L., Chen, L., Dai, W., Wu, Q., & Yuan, S. (2024). Genome mining and biosynthetic pathways of marine-derived fungal bioactive natural products [Review]. *Frontiers in Microbiology*, *Volume 15 - 2024*. https://doi.org/10.3389/fmicb.2024.1520446

Han, M., Wang, Z., Li, Y., Song, Y., & Wang, Z. (2024). The application and sustainable development of coral in traditional medicine and its chemical composition, pharmacology, toxicology, and clinical research. *Frontiers in Pharmacology*, *14*, 1230608.

Harper, C. P., Day, A., Tsingos, M., Ding, E., Zeng, E., Stumpf, S. D., Qi, Y., Robinson, A., Greif, J., & Blodgett, J. A. (2024). Critical analysis of polycyclic tetramate macrolactam biosynthetic gene cluster phylogeny and functional diversity. *Applied and Environmental Microbiology*, *90*(6), e00600-00624.

Hegazi, N. M., Mohamed, T. A., Saad, H. H., Al-Hammady, M. A., Hussien, T. A., Hegazy, M.-E. F., & Gross, H. (2022). Molecular network guided cataloging of the secondary metabolome of selected Egyptian Red Sea Soft Corals. *Marine Drugs*, *20*(10), 630.

Hemmerling, F., & Piel, J. (2022). Strategies to access biosynthetic novelty in bacterial genomes for drug discovery. *Nature Reviews Drug Discovery*, *21*(5), 359-378.

Holland, D. C. (2022). Marine Natural Products Biodiscovery and Meta-analysis of their Bioactivities to Improve their Potential for Drug Discovery.

Hur, J. Y., Jeong, E., Kim, Y. C., & Lee, S. R. (2023). Strategies for natural product discovery by unlocking cryptic biosynthetic gene clusters in fungi. *Separations*, *10*(6), 333.

Ibrahim, J. A. A., Botcha, S., & Prattipati, S. D. (2025). Marine actinomycetes: A promising source of novel therapeutics and pharmaceutical bioactive compounds – A review. *The Microbe*, *7*, 100383. https://doi.org/https://doi.org/10.1016/j.microb.2025.100383

Jamalabadi, M. Y. A. (2025). A Comprehensive Review on Deep Learning for Genomics and AI in Drug Discovery.

Jayawardena, T. U., Merindol, N., Liyanage, N. S., Awwad, F., & Desgagne-Penix, I. (2025). Marine specialized metabolites: Unveiling Nature's chemical treasures from the deep blue. *TRAC Trends in Analytical Chemistry*, *183*, 118097.

Joshi, A., Kumar, A., & Kaushik, V. (2024). Functional genomics and network biology. In *Advances in Bioinformatics* (pp. 71-96). Springer.

Kaur, K., Sharma, V., Kabila, B., & Sidhu, M. C. (2025). The Science of Omics: A Recent Approach for Screening and Enhancement of Bioactive Compounds in Medicinal Plants. In *Biotechnological Innovations for Sustainable Biodiversity and Development* (pp. 59-67). CRC Press.

Kim, H. W., Wang, M., Leber, C. A., Nothias, L.-F., Reher, R., Kang, K. B., van der Hooft, J. J. J., Dorrestein, P. C., Gerwick, W. H., & Cottrell, G. W. (2021). NPClassifier: A Deep Neural Network-Based Structural Classification Tool for Natural Products. *Journal of Natural Products*, *84*(11), 2795-2807. https://doi.org/10.1021/acs.jnatprod.1c00399

Kleigrewe, K., Almaliti, J., Tian, I. Y., Kinnel, R. B., Korobeynikov, A., Monroe, E. A., Duggan, B. M., Di Marzo, V., Sherman, D. H., & Dorrestein, P. C. (2015). Combining mass spectrometric metabolic profiling with genomic analysis: a powerful approach for discovering natural products from cyanobacteria. *Journal of Natural Products*, *78*(7), 1671-1682.

Kumar, A., & Sadashiva, D. N. (2025). The Synergy Of Artificial Intelligence And Big Data Analytics In Accelerating Drug Discovery: From Target Identification To Clinical Trials. *International Journal of Environmental Sciences*, *11*(4s), 161-179.

Kusaczuk, M., Piskorz, W. M., & Domasik, J. (2025a). Marizomib in the therapy of brain tumors—how far did we go and where do we stand? *Pharmacological Reports*, *77*(5), 1177-1195. https://doi.org/10.1007/s43440-025-00739-0

Kusaczuk, M., Piskorz, W. M., & Domasik, J. (2025b). Marizomib in the therapy of brain tumors—how far did we go and where do we stand? *Pharmacological Reports*, 1-19.

Landete, P., Caliman-Sturdza, O. A., Lopez-Martin, J. A., Preotescu, L., Luca, M. C., Kotanidou, A., Villares, P., Iglesias, S. P., Guisado-Vasco, P., Saiz-Lou, E. M., Del Carmen Farinas-Alvarez, M., de Lucas, E. M., Perez-Alba, E., Cisneros, J. M., Estrada, V., Hidalgo-Tenorio, C., Poulakou, G., Torralba, M., Fortun, J., . . . Varona, J. F. (2024). A Phase III Randomized Controlled Trial of Plitidepsin, a Marine-Derived Compound, in Hospitalized Adults With Moderate COVID-19. *Clin Infect Dis*, *79*(4), 910-919. https://doi.org/10.1093/cid/ciae227

Lauritano, C., Ferrante, M. I., & Rogato, A. (2019). Marine natural products from microalgae: An-omics overview. *Marine Drugs*, *17*(5), 269.

Leal, M. C., Puga, J., Serôdio, J., Gomes, N. C. M., & Calado, R. (2012). Trends in the Discovery of New Marine Natural Products from Invertebrates over the Last Two Decades – Where and What Are We Bioprospecting? *PLOS ONE*, *7*(1), e30580. https://doi.org/10.1371/journal.pone.0030580

Leao, T., Castelão, G., Korobeynikov, A., Monroe, E. A., Podell, S., Glukhov, E., Allen, E. E., Gerwick, W. H., & Gerwick, L. (2017). Comparative genomics uncovers the prolific and distinctive metabolic potential of the cyanobacterial genus Moorea. *Proceedings of the National Academy of Sciences*, *114*(12), 3198-3203. https://doi.org/doi:10.1073/pnas.1618556114

Leao, T. F., Clark, C. M., Bauermeister, A., Elijah, E. O., Gentry, E. C., Husband, M., Oliveira, M. F., Bandeira, N., Wang, M., & Dorrestein, P. C. (2021). Quick-start infrastructure for untargeted metabolomics analysis in GNPS. *Nat Metab*, *3*(7), 880-882. https://doi.org/10.1038/s42255-021-00429-0

Li, R., Tang, J., Li, J., Wu, B., Tang, J., Kan, H., Zhao, P., Zhang, Y., Wang, W., & Liu, Y. (2024). Bioactivity-guided isolation of secondary metabolites with antioxidant and antimicrobial activities from Camellia fascicularis. *Foods*, *13*(14), 2266.

Liao, L., Xie, M., Zheng, X., Zhou, Z., Deng, Z., & Gao, J. (2025). Molecular insights fast-tracked: AI in biosynthetic pathway research. *Natural Product Reports*.

Liu, X., & Zhang, W. (2024). Bioinformatics in the Age of Big Data: Leveraging Computational Tools for Biological Discoveries. *Computational Molecular Biology*, *14*.

Lonial, S., Lee, H. C., Badros, A., Trudel, S., Nooka, A. K., Chari, A., Abdallah, A.-O., Callander, N., Lendvai, N., & Sborov, D. (2020). Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *The lancet oncology*, *21*(2), 207-221.

Lotti, A. (2024). *Synthetic biology strategies for (meta) genomic-guided natural product discovery* ETH Zurich].

Louwen, J. J., Medema, M. H., & van der Hooft, J. J. (2023). Enhanced correlation-based linking of biosynthetic gene clusters to their metabolic products through chemical class matching. *Microbiome*, *11*(1), 13.

Martin, L. P., Krasner, C., Rutledge, T., Ibañes, M. L., Fernández-García, E. M., Kahatt, C., Gómez, M. S., & McMeekin, S. (2013). Phase II study of weekly PM00104 (ZALYPSIS(®)) in patients with pretreated

advanced/metastatic endometrial or cervical cancer. *Med Oncol*, *30*(3), 627. https://doi.org/10.1007/s12032-013-0627-3

Martínez, H., Santos, M., Pedraza, L., & Testera, A. M. (2025). Advanced Technologies for Large Scale Supply of Marine Drugs. *Marine Drugs*, *23*(2), 69.

Mayer, A. M. S., Glaser, K. B., Cuevas, C., Jacobs, R. S., Kem, W., Little, R. D., McIntosh, J. M., Newman, D. J., Potts, B. C., & Shuster, D. E. (2010). The odyssey of marine pharmaceuticals: a current pipeline perspective. *Trends in Pharmacological Sciences*, *31*(6), 255-265. https://doi.org/10.1016/j.tips.2010.02.005

Mhlongo, J. K. (2021). Screening of marine bacteria as a source of bioactive secondary metabolites.

Moutinho Cabral, I., Gonçalves, C., Grosso, A. R., & Costa, P. M. (2024). Bioprospecting and marine 'omics': surfing the deep blue sea for novel bioactive proteins and peptides. *Frontiers in Marine Science*, *11*, 1362697.

Mudadla, T., Sharma, G., Mishra, A., & Gola, S. (2024). Multifaceted Landscape of Omics Data. *Bio-Algorithms and Med-Systems*, *20*(1), 22-36.

Newman, D. J., & Cragg, G. M. (2020). Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. *Journal of Natural Products*, *83*(3), 770-803. https://doi.org/10.1021/acs.jnatprod.9b01285

Nothias, L. F., Petras, D., Schmid, R., Dührkop, K., Rainer, J., Sarvepalli, A., Protsyuk, I., Ernst, M., Tsugawa, H., Fleischauer, M., Aicheler, F., Aksenov, A. A., Alka, O., Allard, P. M., Barsch, A., Cachet, X., Caraballo-Rodriguez, A. M., Da Silva, R. R., Dang, T., . . . Dorrestein, P. C. (2020). Feature-based molecular networking in the GNPS analysis environment. *Nat Methods*, *17*(9), 905-908. https://doi.org/10.1038/s41592-020-0933-6

Papapanou, M., Papoutsi, E., Giannakas, T., & Katsaounou, P. (2021). Plitidepsin: Mechanisms and clinical profile of a promising antiviral agent against COVID-19. *Journal of personalized medicine*, *11*(7), 668.

Petek, B. J., & Jones, R. L. (2014). PM00104 (Zalypsis®): a marine derived alkylating agent. *Molecules*, *19*(8), 12328-12335. https://doi.org/10.3390/molecules190812328

Potts, B. C., Albitar, M. X., Anderson, K. C., Baritaki, S., Berkers, C., Bonavida, B., Chandra, J., Chauhan, D., Cusack, J. C., Jr., Fenical, W., Ghobrial, I. M., Groll, M., Jensen, P. R., Lam, K. S., Lloyd, G. K., McBride, W., McConkey, D. J., Miller, C. P., Neuteboom, S. T., . . . Palladino, M. A. (2011). Marizomib, a proteasome inhibitor for all seasons: preclinical profile and a framework for clinical trials. *Curr Cancer Drug Targets*, *11*(3), 254-284. https://doi.org/10.2174/156800911794519716

Puntin, G., Sweet, M., Fraune, S., Medina, M., Sharp, K., Weis, V. M., & Ziegler, M. (2022). Harnessing the power of model organisms to unravel microbial functions in the coral holobiont. *Microbiology and Molecular Biology Reviews*, *86*(4), e00053-00022.

Rahman, N. I. A., Ramzi, M. M., Rawi, N. N., Siong, J. Y. F., Bakar, K., Bhubalan, K., Ariffin, F., Saidin, J., Azemi, A. K., & Ismail, N. (2024). Characterization of antibiofilm compound from marine sponge Stylissa carteri. *Environmental Science and Pollution Research*, *31*(25), 37552-37563.

Raymond, M. J., & Rakotondraibe, H. L. (2025). Recent Updates on Terpenoids and Other Bioactive Constituents of Marine Sponges. *Molecules*, *30*(5), 1112.

Roychowdhury, R., Das, S. P., Gupta, A., Parihar, P., Chandrasekhar, K., Sarker, U., Kumar, A., Ramrao, D. P., & Sudhakar, C. (2023). Multi-omics pipeline and omics-integration approach to decipher plant's abiotic stress tolerance responses. *Genes*, *14*(6), 1281.

Russo, F. F., Nowatzky, Y., Jaeger, C., Parr, M. K., Benner, P., Muth, T., & Lisec, J. (2024). Machine learning methods for compound annotation in non-targeted mass spectrometry—A brief overview of fingerprinting, in silico fragmentation and de novo methods. *Rapid Communications in Mass Spectrometry*, *38*(20), e9876.

Rutz, A., Bittremieux, W., Schmid, R., Cailloux, O., van der Hooft, J. J., & Beniddir, M. A. (2025). Scalability of mass spectrometry-based metabolomics for natural extracts libraries exploration: current status, challenges, and opportunities. *Natural Product Reports*.

Sabol, D. A. (2025). *Libraries' future: intelligent catalogs, digital repositories, artificial intelligence*. Dr. Daniel A. Sabol.

Sadybekov, A. V., & Katritch, V. (2023). Computational approaches streamlining drug discovery. *Nature*, *616*(7958), 673-685.

Sahana, S., Sarkar, J., Mandal, S., Chatterjee, I., Dhar, S., Datta, S., & Mondal, S. (2025). Multi-omics approaches: transforming the landscape of natural product isolation. *Functional & Integrative Genomics*, *25*(1), 132.

Sarkar, J., Singh, R., & Chandel, S. (2025). Understanding LC/MS-Based Metabolomics: A Detailed Reference for Natural Product Analysis. *PROTEOMICS–Clinical Applications*, *19*(1), e202400048.

Satrio, R. D., Fendiyanto, M. H., & Miftahudin, M. (2024). Tools and techniques used at global scale through genomics, transcriptomics, proteomics, and metabolomics to investigate plant stress responses at the molecular level. In *Molecular dynamics of plant stress and its management* (pp. 555-607). Springer.

Schmid, R., Petras, D., Nothias, L.-F., Wang, M., Aron, A. T., Jagels, A., Tsugawa, H., Rainer, J., Garcia-Aloy, M., Dührkop, K., Korf, A.,

Pluskal, T., Kameník, Z., Jarmusch, A. K., Caraballo-Rodríguez, A. M., Weldon, K. C., Nothias-Esposito, M., Aksenov, A. A., Bauermeister, A., . . . Dorrestein, P. C. (2021). Ion identity molecular networking for mass spectrometry-based metabolomics in the GNPS environment. *Nature Communications*, *12*(1), 3832. https://doi.org/10.1038/s41467-021-23953-9

Seibert, G., & Friedrich, B. (2024). Funding as Enabler for Multidisciplinary Research. In *Bioconvergence Revolution: Challenges and Opportunities in Research Productivity* (pp. 43-57). Springer.

Selegato, D. M., Zanatta, A. C., Pilon, A. C., Veloso, J. H., & Castro-Gamboa, I. (2023). Application of feature-based molecular networking and MassQL for the MS/MS fragmentation study of depsipeptides [Original Research]. *Frontiers in Molecular Biosciences*, *Volume 10 - 2023*. https://doi.org/10.3389/fmolb.2023.1238475

Servillera, M., Peña, M., Cabeza, L., Pula, H. J., Prados, J., & Melguizo, C. (2025). Nudibranchs as sources of marine natural products with antitumor activity: a comprehensive review. *Marine Drugs*, *23*(8), 319.

Seyed, M. A., & Ayesha, S. (2021). Marine-derived pipeline anticancer natural products: A review of their pharmacotherapeutic potential and molecular mechanisms. *Future Journal of Pharmaceutical Sciences*, *7*(1), 203.

Shaikovski, G., Casson, A., Severson, K., Zimmermann, E., Wang, Y. K., Kunz, J. D., Retamero, J. A., Oakley, G., Klimstra, D., & Kanan, C. (2024). Prism: A multi-modal generative foundation model for slide-level histopathology. *arXiv preprint arXiv:2405.10254*.

Shehab, W. S., Haikal, H. A., Elsayed, D. A., El-Farargy, A. F., El-Gazzar, A.-R. B., El-Bassyouni, G. T., & Mousa, S. M. (2024). Pharmacokinetic and molecular docking studies to pyrimidine drug using Mn3O4 nanoparticles to explore potential anti-Alzheimer activity. *Scientific Reports*, *14*(1), 15436.

Sheikh, S. A., Bibi, F., & Ali, I. (2025). MICROBIAL METABOLITES AND SECONDARY METABOLISM: BIOCHEMICAL PATHWAYS IN DRUG DISCOVERY. *Pakistan Journal of Medical & Cardiological Review*, *4*(4), 555-603.

Shen, S.-M., Appendino, G., & Guo, Y.-W. (2022). Pitfalls in the structural elucidation of small molecules. A critical analysis of a decade of structural misassignments of marine natural products. *Natural Product Reports*, *39*(9), 1803-1832.

Shetranjiwalla, S., & Ononiwu, A. (2025). Identifying barriers to scaled-up production and commercialization of chitin and chitosan using green technologies: A review and quantitative green chemistry assessment. *International Journal of Biological Macromolecules*, *305*.

Skinnider, M. A., Johnston, C. W., Gunabalasingam, M., Merwin, N. J., Kieliszek, A. M., MacLellan, R. J., Li, H., Ranieri, M. R. M., Webster, A. L. H., Cao, M. P. T., Pfeifle, A., Spencer, N., To, Q. H., Wallace, D. P., Dejong, C. A., & Magarvey, N. A. (2020). Comprehensive prediction of secondary metabolite structure and biological activity from microbial genome sequences. *Nature Communications*, *11*(1), 6058. https://doi.org/10.1038/s41467-020-19986-1

Strashnova, I. V., Mashkova, A., Lisiutin, G., & Ivanytsia, T. V. (2024). Antagonistic activity of actinobacteria isolated from sponges Haliclona spp. Odesa Bay.

Szallasi, A. (2024). Targeting TRPV1 for cancer pain relief: can it work? *Cancers*, *16*(3), 648.

Tan, L. T. (2023). Impact of marine chemical ecology research on the discovery and development of new pharmaceuticals. *Marine Drugs*, *21*(3), 174.

Tenchov, R., & Zhou, Q. A. (2025). Extremophiles: Unlocking Bioactive Compounds and Biotechnological Innovation from Life at the Edge.

Udwary, D. W., Zeigler, L., Asolkar, R. N., Singan, V., Lapidus, A., Fenical, W., Jensen, P. R., & Moore, B. S. (2007). Genome sequencing reveals complex secondary metabolome in the marine actinomycete Salinispora tropica. *Proceedings of the National Academy of Sciences*, *104*(25), 10376-10381. https://doi.org/doi:10.1073/pnas.0700962104

van Der Hooft, J. J., Mohimani, H., Bauermeister, A., Dorrestein, P. C., Duncan, K. R., & Medema, M. H. (2020). Linking genomics and metabolomics to chart specialized metabolic diversity. *Chemical Society Reviews*, *49*(11), 3297-3314.

Vitorino, R. (2024). Transforming clinical research: the power of high-throughput omics integration. *Proteomes*, *12*(3), 25.

Wackett, L. P. (2018). Natural product databases: An annotated selection of World Wide Web sites relevant to the topics in microbial biotechnology. *Microb Biotechnol*, *11*(4), 797-798. https://doi.org/10.1111/1751-7915.13295

Wang, M., Carver, J. J., Phelan, V. V., Sanchez, L. M., Garg, N., Peng, Y., Nguyen, D. D., Watrous, J., Kapono, C. A., & Luzzatto-Knaan, T. (2016). Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking. *Nature Biotechnology*, *34*(8), 828-837.

Wang, M., Chen, L., Zhang, Z., & Wang, Q. (2025). Recent advances in genome mining and synthetic biology for discovery and biosynthesis of natural products. *Critical Reviews in Biotechnology*, *45*(1), 236-256.

Whitesell, J. K., & Minton, M. A. (1987). A novel synthesis of ikarugamycin: the carbocyclic portion. *Journal of the American Chemical Society*, *109*(21), 6403-6408. https://doi.org/10.1021/ja00255a028

Wilson, M. C., Mori, T., Rückert, C., Uria, A. R., Helf, M. J., Takada, K., Gernert, C., Steffens, U. A. E., Heycke, N., Schmitt, S., Rinke, C., Helfrich, E. J. N., Brachmann, A. O., Gurgui, C., Wakimoto, T., Kracht, M., Crüsemann, M., Hentschel, U., Abe, I., . . . Piel, J. (2014). An environmental bacterial taxon with a large and distinct metabolic repertoire. *Nature*, *506*(7486), 58-62. https://doi.org/10.1038/nature12959

Yan, X.-Y., Zhang, L., Yang, Q.-B., Ge, Z.-Y., Liang, L.-F., & Guo, Y.-W. (2023). Genus Litophyton: A hidden treasure trove of structurally unique and diversely bioactive secondary metabolites. *Marine Drugs*, *21*(10), 523.

Yang, Q.-B., Wu, Q., Chen, J.-K., & Liang, L.-F. (2022). The soft coral Sarcophyton trocheliophorum: A warehouse of terpenoids with structural and pharmacological diversity. *Marine Drugs*, *21*(1), 30.

Zhang, M., Otsuki, K., & Li, W. (2023). Molecular networking as a natural products discovery strategy. *Acta Materia Medica*, *2*(2), 126-141.

Zhang, S., Shi, G., Xu, X., Guo, X., Li, S., Li, Z., Wu, Q., & Yin, W.-B. (2024). Global analysis of natural products biosynthetic diversity encoded in fungal genomes. *Journal of Fungi*, *10*(9), 653.

Zhao, W., Zheng, X. D., Tang, P. Y. Z., Li, H. M., Liu, X., Zhong, J. J., & Tang, Y. J. (2023). Advances of antitumor drug discovery in traditional Chinese medicine and natural active products by using multi-active components combination. *Medicinal Research Reviews*, *43*(5), 1778-1808.

Zhou, Q., Hotta, K., Deng, Y., Yuan, R., Quan, S., & Chen, X. (2021). Advances in Biosynthesis of Natural Products from Marine Microorganisms. *Microorganisms*, *9*(12). https://doi.org/10.3390/microorganisms9122551

Zhou, Q., Jia, J., Wang, Y., Chen, R., & Chen, X. (2021). Practical synthesis of phthalascidin and zalypsis antitumor agents. *Tetrahedron Letters*, *86*, 153498.

Zhou, S., Song, X., Zeng, W., & Chen, D. (2025). Targeting Ion Channels for Cancer Therapy: From Pathophysiological Mechanisms to Clinical Translation. *Pharmaceuticals*, *18*(10), 1521.

Zhu, S., Xu, H., Liu, Y., Hong, Y., Yang, H., Zhou, C., & Tao, L. (2025). Computational advances in biosynthetic gene cluster discovery and prediction. *Biotechnology Advances*, 108532.