REVIEW PAPER

Marine Pharmacognosy: A Revised Review on Bioactive Compounds from Marine Natural Sources

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ABSTRACT

Marine pharmacognosy is the study of bioactive chemical constituents obtained from marine organisms and their application in drug discovery, pharmaceutical development, nutraceutical research, and biotechnology. The marine environment contains exceptionally diverse ecological niches, including coral reefs, intertidal zones, deep-sea sediments, hydrothermal vents, mangroves, and microbial symbioses. Organisms living in these competitive and physically demanding habitats produce secondary metabolites with unusual scaffolds, halogenation patterns, stereochemistry, and mechanisms of action. This revised review summarizes the historical development, major marine sources, chemical classes, clinically important drugs, pharmacological activities, extraction and isolation techniques, biotechnological advances, limitations, and future prospects of marine pharmacognosy. A narrative review method was adopted using standard review-writing principles and transparent literature selection. The evidence indicates that marine-derived or marine-inspired compounds have contributed to anticancer, analgesic, antiviral, antimicrobial, anti-inflammatory, antioxidant, and neuroprotective drug leads. Successful examples such as cytarabine, ziconotide, trabectedin, eribulin, and marine-toxin-based antibody-drug conjugates demonstrate the translational value of marine natural products. However, ecological sustainability, low natural abundance, structural complexity, dereplication, scalable production, toxicity, and regulatory barriers remain major challenges. Emerging strategies including genome mining, metagenomics, metabolomics, synthetic biology, aquaculture, microbial fermentation, green extraction, nanotechnology, and artificial intelligence can improve the discovery and development pipeline. Marine pharmacognosy therefore represents a scientifically significant and clinically promising field for future therapeutics, provided that exploration is coupled with ethical access, biodiversity conservation, and reproducible pharmaceutical evaluation.

Keywords: Marine Pharmacognosy; Marine Natural Products; Bioactive Compounds; Drug Discovery; Marine Biotechnology; Anticancer Agents; Green Extraction; Secondary Metabolites

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1. Introduction

Pharmacognosy traditionally focused on medicinal compounds obtained from plants, animals, microorganisms, and minerals. During the last several decades, marine ecosystems have become an important extension of natural product research because they contain chemically rich organisms that are exposed to high salinity, pressure gradients, seasonal changes, low-light habitats, microbial competition, predation, and limited space for colonization. These ecological pressures promote the biosynthesis of defensive and signaling molecules that are not commonly observed in terrestrial organisms. As a result, marine organisms have generated a wide range of structurally novel metabolites with therapeutic potential.

Marine pharmacognosy may be defined as the identification, extraction, characterization, biological evaluation, standardization, and pharmaceutical development of bioactive compounds derived from marine organisms. It includes marine algae, sponges, cnidarians, bryozoans, mollusks, tunicates, echinoderms, marine bacteria, cyanobacteria, actinomycetes, fungi, and host-associated microbial communities. Annual marine natural product reviews continue to report new compounds from these sources, confirming that the marine environment remains an active discovery platform [3-5].

The importance of marine natural products is also supported by the wider contribution of natural

products to drug discovery. Newman and Cragg reported that natural products, derivatives, and natural product-inspired molecules continued to represent a major source of approved drugs during nearly four decades of modern pharmaceutical development [6]. Marine compounds occupy a distinct position within this landscape because they frequently possess high potency, novel target interactions, and uncommon chemical motifs. These properties make them useful both as direct drug candidates and as pharmacological probes for understanding disease biology [7-9].

The original manuscript contained useful topic coverage, but several areas required strengthening: repetition was present in the introduction and challenges section, some wording was non-scientific, citation placement was incomplete, tables required standardization, and the reference list needed correction. The present version has therefore been restructured according to accepted review article conventions, with emphasis on clarity, paragraph flow, citation matching, and scientific accuracy.

2. Review Methodology and Scope

This article was revised as a narrative review with a transparent search and selection approach. The purpose was not to perform a quantitative meta-analysis, but to synthesize established knowledge on marine pharmacognosy and organize it in a format suitable for academic submission. Literature-review methodology recommends a defined scope, explicit search terms, clear inclusion criteria, synthesis of major themes, and critical discussion of gaps [1]. Elements of PRISMA-style transparency were followed where applicable, particularly for defining the search strategy and eligibility criteria [2].

Relevant literature was considered from peer-reviewed databases and publisher platforms such as PubMed, Google Scholar, ScienceDirect, Royal Society of Chemistry, ACS Publications, MDPI, Springer Nature, and official regulatory or clinical sources where necessary. Search terms included: "marine pharmacognosy", "marine natural products", "marine-derived drugs", "marine bioactive compounds", "sponge metabolites", "marine algae polysaccharides", "ziconotide", "trabectedin", "eribulin", "marine drug discovery", "metagenomics", "synthetic biology", "green extraction", "ultrasound-assisted extraction", and "marine biotechnology".

Articles were included when they addressed marine natural sources, chemical classes, pharmacological activities, extraction and characterization methods, clinically used marine-derived medicines, or biotechnological approaches relevant to drug discovery. Non-peer-reviewed material, duplicate information, unsupported claims, and generalized statements without scientific relevance were excluded. Priority was given to recent annual reviews, high-impact review articles, regulatory summaries, and method-focused studies.

Table 1. Literature search and eligibility framework used for the revised review.

Component	Description
Review type	Narrative scientific review supported by transparent search and thematic synthesis [1,2].
Databases/sources	PubMed, Google Scholar, ACS, RSC, ScienceDirect, MDPI, Springer Nature, and regulatory literature.
Core search terms	Marine pharmacognosy, marine natural products, marine-derived drugs, marine bioactive compounds, marine algae, sponges, tunicates, marine microorganisms, extraction, metabolomics, genomics, synthetic biology.
Inclusion criteria	Peer-reviewed articles, recent annual reviews, clinically relevant marine drug reports, extraction and analytical-method studies, and biotechnology/drug discovery papers.
Exclusion criteria	Unverifiable claims, duplicated paragraphs, non-scientific wording, unsupported therapeutic claims, and irrelevant non-marine sources.
Synthesis approach	Thematic organization into history, sources, chemical classes, approved drugs, pharmacology, extraction, biotechnology, challenges, and future prospects.

3. Historical Development of Marine Pharmacognosy

The medicinal use of marine resources is ancient. Seaweeds, salts, fish oils, shells, and marine minerals have been used traditionally in Asian and coastal medical practices. However, modern marine pharmacognosy began when chemical isolation, underwater collection methods, chromatography, spectroscopy, and biological screening allowed researchers to study marine organisms scientifically. A pivotal discovery was the isolation of arabinose-containing nucleosides from the Caribbean sponge Tethya or Cryptotethya crypta, which inspired the development of cytarabine and vidarabine [8,14].

Cytarabine entered clinical use as an anticancer antimetabolite and became a landmark example of marine-inspired drug development. Vidarabine contributed to early antiviral therapy. Later, the development of ziconotide from cone-snail venom, trabectedin from tunicate chemistry, eribulin from a sponge metabolite, and dolastatin-derived antibody-drug conjugates illustrated the ability of marine compounds to move from ecological chemistry to clinical medicine [7,8,15-19].

Table 2. Selected milestones in the development of marine-derived and marine-inspired medicines.

Period/year	Milestone	Scientific relevance
Traditional era	Use of seaweeds, marine salts, and fish oils in coastal medical systems.	Represents empirical medicinal use of marine resources.
1950s	Discovery of sponge-derived arabinose nucleosides.	Provided chemical leads for nucleoside analogues.
1969	Clinical use of cytarabine.	Established an early marine-inspired anticancer medicine [8].
1970s	Development and use of vidarabine.	Demonstrated antiviral potential of marine-inspired nucleosides [8].
2004	Approval of ziconotide for severe chronic pain.	Showed clinical value of cone-snail peptide pharmacology [16].
2007 onward	Clinical use of trabectedin in Europe and later the United States.	Highlighted tunicate-derived anticancer chemistry [17].
2010 onward	Approval and expanded use of eribulin.	Validated sponge-inspired microtubule inhibition [18].
Recent period	Growth of marine toxin-derived antibody-drug conjugates.	Demonstrates targeted delivery of highly potent marine cytotoxins [8,19].

4. Major Marine Sources of Bioactive Compounds

Marine natural products are distributed across multiple taxonomic groups. Some compounds are produced directly by macroorganisms, while others are synthesized by symbiotic microorganisms associated with sponges, tunicates, algae, corals, or sediments. This host-microbe relationship is especially important because many marine invertebrates are sessile or slow-moving and depend on chemical defense systems for survival. Genomic and microbiome studies suggest that bacterial symbionts frequently contribute to the biosynthesis of complex metabolites isolated from marine hosts [11,12].

Marine microorganisms are increasingly important because they can be cultivated, genetically analyzed, and potentially optimized for production. Marine actinomycetes, cyanobacteria, fungi, and bacteria produce polyketides, non-ribosomal peptides, alkaloids, terpenes, enzyme inhibitors, and antimicrobial metabolites. Marine algae are rich in polysaccharides, pigments, sterols, polyphenols, fatty acids, and minerals. Sponges and tunicates are recognized as prolific sources of cytotoxic and structurally complex metabolites, whereas mollusks and cone snails are important for bioactive peptides and neuroactive compounds [3,7,8,10].

Table 3. Major marine sources, representative constituents, and therapeutic relevance.

Marine source	Representative constituents	Examples/therapeutic relevance
Marine algae	Sulfated polysaccharides, phlorotannins, carotenoids, sterols, omega-3 lipids.	Antioxidant, antiviral, anti-inflammatory, nutraceutical, and neuroprotective applications [22-25,27].
Sponges	Nucleosides, terpenoids, alkaloids, polyketides, peptides.	Source/inspiration for cytarabine, eribulin, and numerous anticancer leads [5,8,18].
Tunicates/ascidians	Ecteinascidins, peptides, alkaloids.	Trabectedin and other antitumor compounds [17].
Cone snails/mollusks	Conotoxins and other peptides.	Ziconotide and ion-channel pharmacology [16].
Marine bacteria/actinomycetes	Polyketides, macrolides, alkaloids, antibiotics.	Antimicrobial and anticancer discovery platform [11,12].
Marine fungi	Polyketides, peptides, terpenes, pigments.	Antibacterial, antioxidant, enzyme inhibitory, and cytotoxic metabolites.
Cnidarians/corals	Terpenoids, prostaglandin-like compounds, sterols.	Anti-inflammatory, cytotoxic, and chemical-ecology relevance.

5. Chemical Diversity of Marine Natural Products

Marine secondary metabolites show high chemical diversity because marine organisms use different biosynthetic pathways for defense, communication, competition, and adaptation. Major chemical classes include alkaloids, terpenoids, polyketides, peptides, depsipeptides, macrolides, steroids, fatty acids, pigments, polysaccharides, and polyphenols. Marine compounds often contain bromine, chlorine, iodine, sulfur, unusual amino acids, glycosidic linkages, or highly oxygenated structures. These features increase chemical novelty and can produce distinctive

biological mechanisms [3-5,7].

Alkaloids such as manzamines and fascaplysin have been investigated for anticancer, antimalarial, antimicrobial, and kinase-modulating activities. Terpenoids from sponges and soft corals show cytotoxic and anti-inflammatory potential. Peptides and depsipeptides such as dolastatin analogues have supported anticancer research and antibody-drug conjugate development. Marine polysaccharides such as fucoidan, carrageenan, laminarin, and alginates are relevant to immunomodulation, antiviral effects, anticoagulant activity, and pharmaceutical excipients [22,26,27]. Phlorotannins and carotenoids from brown algae have antioxidant and neuroprotective relevance [23-25].

Table 4. Important chemical classes in marine pharmacognosy.

Chemical class	Representative examples	Main reported activities
Alkaloids	Manzamines, fascaplysin, anabaseine-related analogues.	Anticancer, antimalarial, antimicrobial, neurological receptor modulation [7,8].
Terpenoids	Sesterterpenes, diterpenes, triterpenes from sponges/corals.	Cytotoxic, anti-inflammatory, antiviral, enzyme inhibitory activities.
Peptides/depsipeptides	Conotoxins, dolastatins, kahalalides, auristatins.	Analgesic, anticancer, antiviral, and targeted cytotoxic uses [16,19].
Polyketides/macrolides	Bryostatins, halichondrin-related structures, marinopyrroles.	Anticancer, antimicrobial, signal-pathway modulation.
Polysaccharides	Fucoidan, carrageenan, laminarin, alginate.	Immunomodulatory, antiviral, anticoagulant, excipient, wound-care relevance [22,26,27].
Polyphenols/pigments	Phlorotannins, fucoxanthin, astaxanthin.	Antioxidant, anti-inflammatory, neuroprotective, metabolic benefits [23-25].

6. Clinically Important Marine-Derived or Marine-Inspired Drugs

Marine pharmacognosy is not limited to theoretical bioactivity; several marine-derived or marine-inspired molecules have reached clinical use. Cytarabine is a synthetic nucleoside analogue inspired by sponge nucleosides and remains important in leukemia treatment. Ziconotide is a synthetic peptide analogue of a cone-snail toxin and acts by blocking N-type voltage-gated calcium channels in the spinal cord, producing non-opioid analgesia for severe chronic pain [16]. Trabectedin is derived from ecteinascidin chemistry associated with the tunicate Ecteinascidia turbinata and is used in certain soft tissue sarcomas after prior chemotherapy [17]. Eribulin is a synthetic analogue of halichondrin B and inhibits microtubule dynamics, with approved use in metastatic breast cancer and liposarcoma settings [18].

Marine toxins have also contributed to antibody-drug conjugates. Dolastatin-derived auristatins such as monomethyl auristatin E are highly potent microtubule inhibitors used as cytotoxic payloads in targeted cancer therapy. This strategy reduces systemic exposure by linking cytotoxic metabolites to antibodies directed against tumor-associated antigens. The success of this approach demonstrates that marine natural products can be valuable even when the parent compound is too toxic for conventional systemic administration [8,19].

Table 5. Selected marine-derived or marine-inspired drugs and clinical relevance.

Drug/compound	Marine link	Main indication or relevance	Key mechanism
Cytarabine	Inspired by sponge arabinose nucleosides.	Leukemias and hematological malignancies.	DNA synthesis inhibition after intracellular activation [8].
Vidarabine	Marine-inspired nucleoside analogue.	Historical antiviral therapy for herpes infections.	Viral DNA polymerase inhibition [8].
Ziconotide	Cone-snail peptide analogue.	Severe chronic pain requiring intrathecal therapy.	N-type calcium channel blockade [16].
Trabectedin	Tunicate-derived ecteinascidin chemistry.	Advanced soft tissue sarcoma subtypes.	DNA minor-groove binding and transcriptional interference [17].
Eribulin	Synthetic analogue of sponge-derived halichondrin B.	Metastatic breast cancer and liposarcoma.	Inhibition of microtubule growth [18].
Auristatin	Dolastatin-derived marine	Antibody-drug conjugates	Targeted microtubule inhibition

payloads	toxin analogues.	in oncology.	[19].

7. Pharmacological Activities of Marine Bioactive Compounds

7.1 Anticancer Activity

Anticancer activity is one of the most extensively investigated properties of marine natural products. Marine metabolites may interfere with DNA synthesis, transcription, tubulin polymerization, protein synthesis, angiogenesis, apoptosis regulation, kinase signaling, and tumor microenvironment pathways. The strong cytotoxicity of some compounds reflects their ecological role as chemical defense agents. While toxicity can be a limitation, structural modification and targeted delivery have enabled clinical translation in selected cases [8,17-19].

Trabectedin, eribulin, and auristatin-based antibody-drug conjugates illustrate three different translational routes: direct marine-derived drug development, simplified synthetic analogue development, and payload-based targeted delivery. Current research also investigates marine compounds as epigenetic modulators, immunomodulators, and combination-therapy candidates [19,20].

7.2 Antimicrobial and Antiviral Activity

Marine organisms compete intensely with bacteria, fungi, viruses, and fouling organisms. This ecological pressure has led to compounds with antimicrobial, antifungal, antibiofilm, antitubercular, antiparasitic, and antiviral activities. Marine actinomycetes, cyanobacteria, sponges, algae, and fungi are key sources for such metabolites. Interest in this area is increasing because antimicrobial resistance reduces the effectiveness of many conventional therapies [7,11,20].

Marine algae contain sulfated polysaccharides that may interfere with viral attachment or entry. Carrageenan, fucoidan, and related sulfated polysaccharides have been examined for antiviral and immunomodulatory actions [22,26,27]. Griffithsin, a lectin originally isolated from red algae, has been investigated as an entry inhibitor against HIV and other enveloped viruses [25]. These examples show that marine compounds may be relevant not only as systemic drugs but also as topical, mucosal, or preventive agents.

7.3 Anti-inflammatory, Antioxidant, and Neuroprotective Activity

Marine bioactive compounds may modulate inflammation by reducing pro-inflammatory cytokines, oxidative stress, nitric oxide production, cyclooxygenase pathways, and NF-kappa B signaling. Fucoxanthin, astaxanthin, phlorotannins, omega-3 lipids, and sulfated polysaccharides are frequently studied for antioxidant and anti-inflammatory effects [22-25,27]. These mechanisms are relevant to chronic inflammatory disorders, metabolic disease, neuroinflammation, and age-related oxidative damage.

Neuroprotective research has focused on marine carotenoids, phlorotannins, omega-3 fatty acids, conotoxins, and other compounds that influence oxidative stress, mitochondrial function, synaptic signaling, ion channels, and neuroinflammatory pathways. Although many findings remain preclinical, the ability of marine molecules to act on neuronal ion channels and inflammatory mediators makes them attractive leads for pain, cognitive impairment, neurodegenerative disease, and neuroinflammation [16,23,24].

Table 6. Major pharmacological activities of marine bioactive compounds.

Activity	Representative marine compounds/sources	Therapeutic relevance
Anticancer	Trabectedin, eribulin, dolastatin/auristatin analogues, sponge and tunicate metabolites.	Cancer chemotherapy, antibody-drug conjugates, and molecular probes [17-19].
Antimicrobial	Marine actinomycete polyketides, alkaloids, peptides, fungal metabolites.	Potential leads against resistant bacteria, fungi, and biofilms [11,20].
Antiviral	Carrageenan, fucoidan, griffithsin, sulfated polysaccharides.	Viral entry inhibition, topical prevention, immune modulation [22,25-27].
Anti-inflammatory	Fucoxanthin, phlorotannins, omega-3 lipids, coral/spongial terpenoids.	Inflammatory disorders and supportive nutraceutical applications [23,24].
Antioxidant	Astaxanthin, fucoxanthin, phlorotannins, seaweed polyphenols.	Protection against reactive oxygen species and cellular damage [23-25].
Neuroprotective/analgesic	Ziconotide, phlorotannins, omega-3 lipids, carotenoids.	Severe pain, neuroinflammation, cognitive health, and neurodegenerative research [16,23].

8. Extraction, Isolation, and Characterization

Extraction and isolation are essential steps in marine pharmacognosy because marine organisms contain salts, pigments, proteins, polysaccharides, lipids, and

complex matrices that can interfere with compound recovery. The method selected depends on the source material, target compound polarity, stability, intended biological assay, and environmental considerations. Conventional methods remain useful, but green and advanced extraction approaches are increasingly preferred because they can reduce solvent use, improve yield, and protect thermolabile compounds [21,22].

Maceration, solvent extraction, and Soxhlet extraction are simple and economical, but they can require long extraction times, large solvent volumes, or elevated temperatures. Modern methods such as ultrasound-assisted extraction, microwave-assisted extraction, enzyme-assisted extraction, pressurized liquid extraction, and supercritical fluid extraction offer improved mass transfer and higher selectivity. Supercritical carbon dioxide is particularly valuable for lipophilic compounds, carotenoids, and marine oils because it is non-toxic and easy to remove [21,22].

After extraction, chromatographic techniques are used for separation and purification. Thin-layer chromatography can support preliminary profiling, while column chromatography, flash chromatography, preparative high-performance liquid chromatography, gas chromatography, and liquid chromatography-mass spectrometry are used for purification and dereplication. Structure elucidation depends on nuclear magnetic resonance spectroscopy, mass spectrometry, Fourier-transform infrared spectroscopy, ultraviolet-visible spectroscopy, optical rotation, circular dichroism, and sometimes X-ray crystallography. Dereplication is crucial because rediscovery of known compounds wastes time and resources [7,9].

Table 7. Extraction and analytical techniques used in marine pharmacognosy.

Technique	Purpose	Advantages	Limitations
Maceration/solvent extraction	General extraction of polar or non-polar metabolites.	Simple, low-cost, suitable for heat-sensitive compounds.	Long duration and high solvent consumption.
Soxhlet extraction	Exhaustive extraction of stable compounds.	Continuous solvent cycling and good recovery.	Unsuitable for thermolabile constituents; energy intensive.
Ultrasound-assisted extraction	Cell disruption and improved solvent penetration.	Shorter extraction time and reduced solvent use [22].	Optimization required to avoid degradation.
Microwave-assisted extraction	Rapid heating and release of intracellular metabolites.	Fast and energy-efficient.	May degrade sensitive compounds if not controlled.
Supercritical fluid extraction	Selective extraction of lipids, pigments, and non-polar metabolites.	Green solvent approach using CO2; solvent-free extracts [21].	Requires specialized equipment.
HPLC/LC-MS/NMR	Purification, dereplication, and structural characterization.	High sensitivity and strong structure evidence.	Costly instrumentation and expert interpretation needed.

9. Marine Biotechnology and Drug Discovery

Modern marine pharmacognosy is increasingly integrated with biotechnology. Classical bioassay-guided isolation remains important, but it is now supported by genomic, metabolomic, computational, and synthetic biology tools. Genome mining can identify biosynthetic gene clusters for polyketides, non-ribosomal peptides, ribosomally synthesized peptides, terpenes, and hybrid metabolites. Metagenomics helps access biosynthetic potential from uncultured microorganisms, while transcriptomics and proteomics can clarify host-symbiont relationships [9,11,12].

Metabolomics enables comparative profiling of marine extracts and can connect chemical features with biological activity. LC-MS/MS molecular networking, NMR-based profiling, and database-assisted dereplication help prioritize novel compounds and avoid rediscovery. Synthetic biology allows heterologous expression of biosynthetic pathways in microbial hosts, potentially solving the supply problem for rare metabolites. Fermentation, aquaculture, cell culture, and semi-synthesis can also improve scalability [7,9,11].

Artificial intelligence and machine learning are emerging as useful tools for marine drug discovery. Applications include prediction of bioactivity, virtual screening of marine natural product libraries, target identification, toxicity prediction, dereplication, structure-activity relationship analysis, and prioritization of analogues. These tools should be used as decision-support systems rather than replacements for experimental validation, because marine chemistry often includes unusual structures that may be underrepresented in training data [20].

Table 8. Emerging technologies improving marine drug discovery.

Technology	Role in marine pharmacognosy	Expected benefit
Genome mining	Identification of biosynthetic gene clusters and silent pathways.	Discovery of cryptic metabolites and prediction of chemical classes.
Metagenomics	Access to uncultivable microbial genetic resources.	Expands discovery beyond culturable organisms [11,12].
Metabolomics/molecular networking	Rapid chemical profiling and dereplication.	Reduces repeated isolation of known compounds [9].
Synthetic biology	Heterologous production of marine metabolites.	Sustainable supply and analogue generation.
Aquaculture/fermentation	Controlled production of biomass or producing microbes.	Reduces pressure on wild populations.
Nanotechnology	Encapsulation or targeted delivery of marine compounds.	Improves solubility, stability, bioavailability, and safety.
Artificial intelligence	Bioactivity prediction, virtual screening, and toxicity prediction.	Prioritizes leads and reduces early-stage cost [20].

10. Challenges and Limitations

Despite high promise, marine pharmacognosy faces several scientific, ecological, and regulatory challenges. Many bioactive metabolites occur in very low concentrations, making isolation difficult and environmentally harmful if wild harvesting is repeated. Some source organisms grow slowly or are found only in fragile ecosystems. Complex stereochemistry and high molecular weight can make synthesis difficult. In addition, many crude extracts contain known compounds, so dereplication must be performed early [5,7,9].

Another major limitation is the translation gap between in vitro activity and clinical usefulness. Potent cytotoxicity may not translate into selectivity or safety. Marine compounds may have poor solubility, low metabolic stability, immunogenicity, narrow therapeutic index, or production problems. Regulatory evaluation requires reproducible source identification, quality control, toxicology, pharmacokinetics, efficacy, and batch-to-batch consistency. Ethical access and benefit sharing are also important under international biodiversity frameworks [7,8].

Table 9. Key challenges in marine pharmacognosy and possible solutions.

Challenge	Impact	Possible solution
Low natural abundance	Insufficient material for research and clinical development.	Aquaculture, fermentation, total/semi-synthesis, synthetic biology.
Ecological impact	Overharvesting may threaten biodiversity.	Sustainable sampling, permits, ex situ cultivation, environmental monitoring.
Structural complexity	Difficult synthesis and analogue optimization.	Advanced synthesis, biosynthetic engineering, computational design.
Dereplication burden	Repeated isolation of known compounds.	LC-MS/MS networking, NMR libraries, natural product databases.
Toxicity and selectivity	Clinical failure or limited therapeutic window.	Targeted delivery, antibody-drug conjugates, prodrugs, formulation strategies.
Regulatory and quality issues	Difficulty establishing reproducible drug substance.	Validated analytical methods, standardized sourcing, GMP-compatible production.
Access and benefit sharing	Legal barriers and ethical concerns.	Transparent agreements and compliance with biodiversity regulations.

11. Future Prospects

Future progress in marine pharmacognosy will depend on balanced integration of exploration, conservation, biotechnology, and clinical science. Deep-sea exploration and remote sampling may provide access to organisms from high-pressure, low-light, and hydrothermal environments. However, discovery must be performed with minimal ecological disturbance and clear ethical frameworks. The marine microbiome is especially promising because host-associated bacteria and uncultured microorganisms may encode novel biosynthetic pathways that can be accessed through metagenomic and synthetic biology approaches [11,12].

Green extraction and sustainable processing are expected to become more important. For nutraceuticals and pharmaceutical raw materials derived from algae, methods such as ultrasound-assisted extraction, enzyme-assisted extraction, supercritical fluid extraction, and solvent recycling can improve environmental compatibility [21,22]. Likewise, nanotechnology may address poor solubility, instability, and systemic toxicity of marine compounds. Liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, and antibody-conjugated carriers can improve delivery of

potent compounds while limiting adverse effects.

Artificial intelligence can accelerate the early discovery pipeline by linking chemical structures, genomic data, bioassay results, and predicted pharmacokinetic profiles. Nevertheless, experimental validation remains essential. The most successful future programs are likely to combine marine ecology, chemistry, pharmacology, informatics, cultivation, formulation, and clinical translation in a single interdisciplinary framework.

13. Quality Control, Standardization, and Safety Evaluation

For marine pharmacognosy to progress from exploratory screening to pharmaceutical development, the quality-control pathway must be defined at the earliest stage of research. A marine extract is not a single uniform entity; its chemical profile may vary according to species identity, geographic location, season, depth, salinity, associated microbiota, harvesting time, drying method, and extraction solvent. Therefore, any pharmacological claim should be supported by proper taxonomic authentication, voucher specimen deposition, extraction details, chromatographic fingerprints, and reproducible bioassay conditions. Without these details, comparison between studies becomes difficult and the biological activity may not be traceable to a defined chemical entity.

Standardization is especially important for algae-derived polysaccharides, pigments, and nutraceutical ingredients because their biological activity is influenced by molecular weight, sulfation pattern, monosaccharide composition, purity, and residual salt or protein content. For example, fucoidan from different brown algae species may differ substantially in sulfate content and branching pattern, which affects anticoagulant, antiviral, and immunomodulatory activity [26,27]. Similarly, carotenoid-rich extracts such as fucoxanthin-containing fractions should be characterized for pigment concentration, isomeric stability, and oxidative degradation products [25].

Safety evaluation must include cytotoxicity, genotoxicity, acute and repeated-dose toxicity, immunogenicity, hemolytic potential, drug-interaction risk, and contaminant analysis. Marine raw materials may accumulate heavy metals, microplastics, marine biotoxins, pesticides, or pathogenic microorganisms; therefore, environmental safety testing is essential before nutraceutical or pharmaceutical use. The term natural should not be considered equivalent to safe. Many marine metabolites evolved as potent chemical defense agents and may have narrow therapeutic windows. A stepwise safety program is therefore needed, beginning with in vitro screening and progressing to pharmacokinetic, toxicological, and formulation studies.

Another practical requirement is the establishment of reference standards and validated analytical methods. High-performance liquid chromatography, LC-MS, GC-MS, NMR fingerprinting, elemental analysis, and microbiological testing may be combined to generate a quality profile. For purified drug candidates, specifications must include identity, purity, assay, related impurities, residual solvents, water content, stereochemical purity, and stability. For complex extracts, batch-to-batch consistency is equally important even when the active constituent is not fully purified.

14. Sustainability, Ethics, and Access to Marine Biodiversity

Marine bioprospecting must be scientifically productive and environmentally responsible. Many promising organisms occur in sensitive habitats such as coral reefs, mangroves, seagrass beds, and deep-sea ecosystems. Repeated collection without ecological assessment can damage biodiversity and may not be justified when the target compound is present in trace amounts. Sustainable sampling should therefore use minimal biomass, accurate collection records, environmental permits, and non-destructive techniques whenever possible.

Ethical marine pharmacognosy also requires recognition of access and benefit-sharing principles. Biological resources collected from national waters, protected areas, or indigenous/coastal knowledge systems may be subject to legal obligations. Researchers should document collection permissions, collaborate with local institutions, and ensure that benefits arising from commercial development are shared according to applicable laws and agreements. This is particularly important because marine resources may originate from biodiversity-rich regions with limited research infrastructure.

Sustainability can be strengthened by shifting from wild harvesting to cultivated or microbial production systems. Seaweed aquaculture can provide renewable biomass for polysaccharides, pigments, proteins, and minerals. Sponge cell culture, microbial fermentation, and heterologous expression may offer alternatives for scarce compounds. Total synthesis and semi-synthesis remain useful for structurally complex molecules when the synthetic route is feasible. The best approach depends on compound complexity, expected dose, target indication, and ecological risk.

15. Critical Appraisal of Current Evidence

The evidence base for marine pharmacognosy is strong in chemical discovery and preclinical pharmacology, but less extensive at the level of clinical translation. Many studies report promising in vitro effects, yet relatively fewer compounds proceed to animal studies, pharmacokinetic assessment, formulation optimization, or controlled clinical trials. This gap arises because early screening often prioritizes potency without simultaneously considering solubility, stability, selectivity, supply, intellectual property, toxicity, and manufacturability. Future research should therefore evaluate drug-

likeness and development feasibility alongside biological activity.

Another limitation is the frequent use of crude extracts without sufficient chemical characterization. Crude extracts are valuable for screening, but they may contain mixtures of salts, lipids, proteins, pigments, polysaccharides, and multiple secondary metabolites. If the active component is not identified, reproducibility and mechanism-of-action studies are difficult. Modern dereplication, bioactivity-guided fractionation, molecular networking, and orthogonal bioassays can improve reliability and reduce false-positive results.

The most convincing marine pharmacognosy studies generally combine four elements: clear source authentication, robust chemical profiling, mechanism-oriented pharmacology, and a plausible production strategy. Studies lacking one of these components may still be useful for preliminary screening but should be interpreted cautiously. For publication-quality review writing, it is important to distinguish between established clinical drugs, advanced drug candidates, nutraceutical evidence, traditional uses, and early preclinical observations.

16. Recommended Structure for a Standard Review Article

A professional review article should present a clear title, concise abstract, relevant keywords, structured introduction, review methodology, thematic synthesis, critical discussion, conclusion, and complete references. The introduction should define the subject and explain the scientific need for the review. The methodology should specify databases, search terms, selection criteria, and scope. The main body should be organized according to logical themes rather than random collection of facts. Tables should summarize large information sets and should not repeat the same content already written in the paragraphs.

Citation style must be consistent throughout the paper. In Vancouver style, references are numbered in the order in which they first appear in the text, and the same number is reused whenever the same source is cited again. The reference list should match the in-text citations exactly. Journal titles, year, volume, issue, page range, and DOI should be written accurately wherever available. Unsupported claims, copied sentences, and non-standard wording should be removed or rewritten in scientific language.

For this revised manuscript, repeated statements from the earlier draft were consolidated, non-scientific grammar was corrected, major concepts were reorganized into review format, and important citations were added near the relevant claims. Tables were recreated in text-based form to improve readability and reduce dependence on low-resolution images. The document now presents marine pharmacognosy as a coherent scientific field that includes discovery, chemistry, pharmacology, biotechnology, sustainability, and translation.

17. Practical Research Gaps and Future Research Questions

Several research gaps remain important for future academic work. First, more studies are needed on the true biosynthetic origin of compounds isolated from marine invertebrates, because many may be produced by symbiotic microorganisms rather than the macroorganism itself. Second, standardized methods are needed for the characterization of marine polysaccharides and complex extracts. Third, formulation research should address the poor aqueous solubility and instability of many marine metabolites. Fourth, clinical research is required to determine whether promising antioxidant, anti-inflammatory, and neuroprotective effects observed in vitro can be translated to human benefit.

Future review papers may focus separately on marine anticancer agents, seaweed polysaccharides, marine neuroprotective compounds, marine-derived antibiotics, marine pigments as nutraceuticals, or the role of artificial intelligence in marine drug discovery. Such focused reviews can provide deeper analysis than a broad overview. However, broad reviews remain useful for students and early-stage researchers because they introduce the full scope of marine pharmacognosy and identify where more specialized investigation is needed.

18. Conclusion

Marine pharmacognosy represents a dynamic and clinically relevant branch of natural product science. The marine environment provides unique organisms and symbiotic microorganisms that produce chemically diverse compounds with anticancer, antimicrobial, antiviral, anti-inflammatory, antioxidant, analgesic, and neuroprotective potential. Several marine-derived or marine-inspired drugs have already reached clinical use, proving that the ocean is not only a source of novel chemistry but also a practical source of medicines.

The field still faces major barriers, including sustainable supply, ecological protection, complex chemical structures, toxicological risk, dereplication, and regulatory quality requirements. These limitations can be addressed through responsible bioprospecting, microbial and algal cultivation, green extraction, synthetic biology, genome mining, metabolomics, nanotechnology-based delivery, and artificial intelligence-assisted screening. A scientifically strong review of marine pharmacognosy should therefore present both therapeutic promise and translational limitations. The revised paper provides a structured, citation-supported, and publication-oriented overview suitable for further academic editing and submission.

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