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MARINE-DERIVED ANTICOAGULANTS: A REVIEW OF MECHANISMS AND THERAPEUTIC POTENTIAL

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Abstract
Marine ecosystems represent a structurally diverse reservoir of bioactive anticoagulant compounds. This review synthesizes advances in marine-derived anticoagulants published between January 2020 and December 2025. A structured literature search was conducted exclusively in the Scopus, Pubmed and ScieceDirect database, with the final search performed in January 2026. Peer-reviewed articles published in English were screened using predefined inclusion and exclusion criteria. Eligible studies investigated marine organisms including algae, echinoderms, mollusks, bacteria, and marine symbionts and reported structural characterization, mechanistic evaluation, pharmacological profiling, or translational relevance. Conference abstracts, editorials, non-marine studies, and articles lacking mechanistic or structural data were excluded. Recent evidence highlights sulfated polysaccharides, glycosaminoglycans, peptides, and engineered analogues as principal marine-derived anticoagulant candidates. These compounds primarily act through potentiation of antithrombin III/ATIII and heparin cofactor II/HCII as well as selective inhibition of intrinsic pathway factors such as factor XIa and factor XIIa. Advances in green extraction technologies, controlled sulfation chemistry, purification strategies, and nanodelivery systems have improved structural reproducibility and pharmacokinetic performance. Emerging preclinical findings suggest reduced hemorrhagic risk compared with conventional heparins alongside additional antiviral and immunomodulatory properties. Nevertheless, structural heterogeneity, limited oral bioavailability, sustainability constraints, and regulatory challenges remain critical barriers to clinical translation. Integration of advanced structural analytics, synthetic biology, and precision pharmacology will be essential to advance marine-derived anticoagulants toward safe and standardized therapeutic application.
Keyword: *Factor XIa inhibitors; Intrinsic coagulation pathway; Marine-derived anticoagulants; Sulfated polysaccharides; Translational pharmacology*.

Abstrak
Ekosistem laut merupakan sumber yang sangat beragam secara struktural dalam menyediakan senyawa antikoagulan bioaktif. Tinjauan ini mensintesis perkembangan penelitian mengenai antikoagulan turunan laut yang dipublikasikan antara Januari 2020 hingga Desember 2025. Penelusuran literatur terstruktur dilakukan secara eksklusif melalui basis data Scopus, Pubmed dan ScienceDirect dengan pencarian terakhir dilaksanakan pada Januari 2026. Artikel yang telah melalui proses penelaahan sejawat dan dipublikasikan dalam bahasa Inggris diseleksi berdasarkan kriteria inklusi dan eksklusi yang telah ditetapkan sebelumnya. Studi yang memenuhi syarat meneliti organisme laut, termasuk alga, ekinodermata, moluska, bakteri, dan simbion laut, serta melaporkan karakterisasi struktur, evaluasi mekanistik, profil farmakologis, atau relevansi translasional. Abstrak konferensi, editorial, studi non-kelautan, serta artikel yang tidak menyajikan data struktural atau mekanistik dikeluarkan dari analisis. Bukti terkini menunjukkan bahwa polisakarida tersulfatasi, glikosaminoglikan, peptida, dan analog rekayasa merupakan kandidat utama antikoagulan turunan laut. Senyawa-senyawa tersebut bekerja terutama melalui peningkatan aktivitas antitrombin III (ATIII) dan heparin cofactor II (HCII), serta melalui penghambatan selektif faktor jalur intrinsik seperti faktor XIa dan faktor XIIa. Perkembangan teknologi ekstraksi ramah lingkungan, strategi sulfatasi terkontrol, metode pemurnian, dan sistem penghantaran berbasis nanoteknologi telah meningkatkan reprodusibilitas struktur dan kinerja farmakokinetik. Temuan praklinis menunjukkan potensi risiko perdarahan yang lebih rendah dibandingkan heparin konvensional, disertai aktivitas antivirus dan imunomodulator tambahan. Meskipun demikian, heterogenitas struktural, keterbatasan bioavailabilitas oral, kendala keberlanjutan sumber daya, dan tantangan regulasi masih menjadi hambatan utama dalam translasi klinis. Integrasi analitik struktur lanjutan, biologi sintetik, dan farmakologi presisi diperlukan untuk mendorong pengembangan antikoagulan turunan laut yang aman dan terstandarisasi secara terapeutik.
Kata kunci: Inhibitor Faktor XIa; Jalur Koagulasi Intrinsik; Antikoagulan Turunan Laut; Polisakarida Tersulfatasi; Farmakologi Translasional.

INTRODUCTION

Thrombotic disorders remain a leading cause of global morbidity and mortality, contributing substantially to cardiovascular, cerebrovascular, and inflammatory disease burden. Although conventional anticoagulants such as unfractionated heparin, low molecular weight heparins (LMWH), and direct oral anticoagulants (DOACs) are clinically effective, their use is frequently limited by bleeding risk, drug–drug interactions, interindividual variability, and safety concerns in specific patient populations (Fredenburgh & Weitz, 2021; Fu et al., 2024; Kitano et al., 2025; Krishnaswamy et al., 2025; Z. Liu et al., 2022; Qian et al., 2024). These limitations have intensified the search for safer and more selective anticoagulant agents with improved therapeutic indices (Fu et al., 2024; Qian et al., 2024).

Marine ecosystems constitute one of the most chemically diverse environments on Earth. The unique physicochemical pressures of marine habitats have driven the evolution of structurally distinctive metabolites, including sulfated polysaccharides, glycosaminoglycans, peptides, and heparinoid-like molecules (Dwivedi & Pomin, 2020; K. Li et al., 2025). These compounds exhibit diverse mechanisms of coagulation modulation, including potentiation of endogenous serine protease inhibitors and selective inhibition of intrinsic pathway factors such as factor XIa and factor XIIa (Ouyang et al., 2024; Qin et al., 2023; W. Zhang et al., 2022). Advances in analytical chemistry, structural characterization, and biotechnological processing have further accelerated the identification and functional evaluation of marine-derived anticoagulant candidates (Koh et al., 2025; Naseem et al., 2025; Qin et al., 2025).

Previous reviews, including the seminal work by (Dwivedi & Pomin, 2020), established the foundational understanding of marine antithrombotic agents and their structural diversity. More recently, (K. Li et al., 2025) provided an updated synthesis emphasizing diversity and structure–activity relationships of marine anticoagulant polysaccharides. Since 2020, the field has progressed beyond structural cataloging toward refined structure–activity analyses, intrinsic pathway–selective inhibition strategies such as factor XIa and factor XIIa targeting, controlled sulfation engineering, nanodelivery integration, and translational considerations encompassing sustainability and regulatory frameworks (Babuty et al., 2025; Herrera Barragán et al., 2022; Koh et al., 2025; Ouyang et al., 2024). To date, limited reviews have integrated these post-2020 structural, mechanistic, technological, and translational advances within a single consolidated framework.

Accordingly, this review aims to synthesize advances in marine-derived anticoagulant compounds published between 2020 and 2025. The specific objectives are to identify major marine sources and structurally characterized candidates, analyze structure–activity relationships and molecular mechanisms, assess pharmacological and translational evidence, and highlight critical research gaps and future development pathways.

METHODS

This article was designed as a narrative review supported by a structured literature search, rather than a systematic review or meta-analysis. The objective was to provide a comprehensive and critical synthesis of post-2020 advances in marine-derived anticoagulants, with emphasis on structural, mechanistic, and translational developments.

A structured search was conducted in the Scopus, PubMed, and ScienceDirect databases to ensure broad coverage of peer-reviewed international publications. The search encompassed articles published between January 2020 and December 2025, with the final search performed in January 2026. Keyword combinations included “marine-derived” OR “marine polysaccharide”

OR “sulfated polysaccharide” OR “heparinoid” AND “anticoagulant” OR “antithrombotic” OR “factor XIa inhibitor” OR “intrinsic pathway.” Boolean operators were applied, and searches were restricted to title, abstract, and keyword fields to enhance relevance.

Articles were selected based on conceptual relevance to the objectives of this narrative synthesis. Eligible publications were peer-reviewed articles written in English and published within the predefined time frame. Studies investigating marine-derived organisms, including algae, echinoderms, mollusks, marine bacteria, or marine symbionts, were considered if they reported structural characterization, mechanistic evaluation, pharmacological activity in vitro or in vivo, or translational and formulation perspectives. Both original research articles and review papers were included to support contextual and comparative discussion.

Publications were excluded if they focused exclusively on non-marine sources; were conference abstracts, editorials, commentaries, or non-peer-reviewed documents; lacked structural or mechanistic data relevant to anticoagulant activity; or were published outside the defined period. As this work represents a narrative review, formal risk-of-bias assessment, quantitative data extraction, and PRISMA flow diagram reporting were not performed.

RESULTS AND DISCUSSION

Marine Sources and Bioactive Compounds

The marine ecosystem constitutes a highly dynamic biochemical reservoir, characterized by extraordinary taxonomic diversity and structurally unique secondary metabolites. Among marine-derived anticoagulants, algae and invertebrates represent the most extensively studied and pharmacologically promising sources. Their metabolites, particularly sulfated polysaccharides and heparinoid-like molecules, demonstrate diverse mechanisms of coagulation modulation and offer potential advantages in safety and structural variability compared to conventional mammalian anticoagulants (J. Chen et al., 2022; Pringgenies et al., 2025)

Algae (Red, Green, Brown)

Marine macroalgae constitute the most structurally diverse source of sulfated anticoagulant polysaccharides. Brown algae-derived fucoidans and galactofucans, red algal sulfated galactans and carrageenans, and green algal ulvans differ in backbone composition and sulfation topology; however, their anticoagulant activity converges mechanistically through potentiation of antithrombin (AT) and/or heparin cofactor II (HCII), resulting in thrombin (FIIa) and factor Xa (FXa) inhibition (Bento et al., 2023; J. Chen et al., 2021; Felix et al., 2025; Qin et al., 2020; Yang et al., 2024).

Comparative analyses indicate that anticoagulant efficacy increases proportionally with sulfate density and molecular weight, although not linearly. Higher sulfation enhances electrostatic interaction with coagulation proteases, yet excessive sulfation may broaden target engagement and potentially increase bleeding liability. Similarly, increased molecular weight strengthens multivalent binding to AT or HCII but may alter pharmacokinetic behavior. Thus, structural heterogeneity functions as a tunable determinant of potency–safety balance rather than mere compositional variability. Cross-species differences further reveal pathway-oriented modulation. Brown algal fucoidans, enriched in 2-O and 3-O sulfated fucose residues, preferentially enhance thrombin and FXa inhibition, whereas green and red algal galactans with distinct sulfation positions modulate intrinsic pathway components to varying degrees (Ciancia et al., 2020; Punjamgod et al., 2026) .

These observations indicate that sulfation topology, not only sulfate quantity, determines whether activity is predominantly intrinsic-pathway–selective or broadly anticoagulant.

Sea Cucumbers

Holothurians are a rich source of fucosylated chondroitin sulfate (FCS) and other marine glycosaminoglycans with potent anticoagulant and antithrombotic activities. FCS exhibits a unique backbone of chondroitin sulfate decorated with sulfated fucose branches, conferring strong interactions with intrinsic pathway factors and thrombin inhibition pathways. Compared to mammalian heparin, FCS often demonstrates robust antithrombotic efficacy in experimental models with differentiated mechanistic profiles, including modulation of the intrinsic tenase complex (Felix et al., 2025; Lv et al., 2024).

Importantly, experimental comparisons suggest that FCS achieves strong antithrombotic effects while maintaining a mechanistic profile that is not identical to mammalian heparin. This indicates that branching architecture and sulfated fucose positioning introduce alternative binding geometries, thereby expanding the spectrum of coagulation targets and potentially modifying hemorrhagic risk

Sponges, Corals, and Mollusks

Marine invertebrates such as sponges, corals, and mollusks produce chemically diverse bioactive metabolites, including steroids, alkaloids, peptides, and heparinoid-like polysaccharides. These compounds frequently exhibit multitarget pharmacological profiles, combining anticoagulant properties with antiviral, anti-inflammatory, or immunomodulatory effects. Such pleiotropic activity broadens their translational relevance, particularly in thromboinflammatory conditions where coagulation and inflammation intersect (Bento et al., 2023; J. Chen et al., 2022; Du et al., 2020).

From a mechanistic standpoint, such pleiotropy is particularly relevant in thromboinflammatory conditions, where coagulation activation and inflammatory signaling are tightly coupled. The ability of certain marine metabolites to modulate both protease-driven clot formation and inflammatory mediators suggests a systems-level therapeutic advantage compared to single-target anticoagulants

Marine Bacteria

Marine microorganisms have emerged as sustainable and scalable sources of anticoagulant candidates. Exopolysaccharides (EPS) derived from marine bacteria can be chemically modified, particularly through sulfation, to enhance anticoagulant potency. These microbial polysaccharides represent promising non-animal alternatives that address safety and supply concerns associated with animal-derived heparins. Structural engineering strategies further support the optimization of anticoagulant activity and selectivity (Babuty et al., 2025).

Unlike naturally occurring animal-derived heparins, microbial EPS provide scalable and structurally modifiable platforms. Through deliberate adjustment of sulfate density and chain length, anticoagulant potency and pathway selectivity can be systematically optimized. Therefore, microbial systems shift the paradigm from passive natural product isolation toward rational structural engineering.

Novel Species and Compounds (2020–2025)

Recent investigations conducted between 2020 and 2025 have led to the identification of several novel marine-derived anticoagulant candidates characterized by distinct structural architectures and differentiated mechanistic profiles. These discoveries not only expand the taxonomic spectrum of anticoagulant-producing organisms but also highlight the evolving sophistication of structural and functional analyses applied in marine pharmacology.

Codium fragile, a green alga, has been reported to produce a sulfated galactoarabinan designated CZS-0-1. This compound demonstrates dual inhibitory activity against thrombin (FIIa)

and factor Xa (FXa), indicating a capacity to modulate both the common coagulation pathway and key enzymatic effectors of fibrin formation. The presence of sulfate groups and specific carbohydrate linkages appears to contribute to its high-affinity interactions with coagulation factors, reinforcing the importance of fine structural determinants in anticoagulant potency (Peipei et al., 2024).

Similarly, Chaetomorpha aerea, another green algal species, yields PCA, a structurally related sulfated galactoarabinan. PCA has been shown to suppress intrinsic coagulation factors while potentiating thrombin inhibition, thereby demonstrating pathway-oriented modulation of coagulation cascades. This selective targeting of intrinsic pathway components suggests potential therapeutic relevance in conditions where intrinsic pathway hyperactivation predominates (Qin et al., 2023).

Beyond macroalgae, marine invertebrates have also contributed innovative biomaterials. From the cuttlefish Sepia kobiensis, nanochitosan derivatives have been developed and evaluated for anticoagulant activity. The nanoscale configuration of this biopolymer may enhance surface interactions with coagulation proteins and improve bioavailability, indicating that nanostructured marine polysaccharides could represent a promising direction for next-generation anticoagulant design and delivery systems (Thoke et al., 2025).

In the bivalve mollusk Meretrix lusoria, a heparinoid compound has been isolated and characterized with demonstrable anticoagulant effects. Notably, this compound exhibits reduced hemorrhagic risk compared to conventional heparin, suggesting a potentially improved therapeutic index. Structural differences in sulfation pattern and backbone composition may underlie this favorable safety profile, emphasizing the value of marine-derived structural diversity in mitigating adverse bleeding complications (J. Chen et al., 2022).

Collectively, these findings underscore the expanding chemical and mechanistic diversity of marine-derived anticoagulant molecules. Continuous advances in structural elucidation techniques, controlled sulfation chemistry, and mechanistic evaluation are revealing compounds with increasingly refined activity profiles and enhanced translational potential. Such progress reinforces the strategic importance of marine biodiversity as a platform for innovation in antithrombotic drug discovery and development.

Table 1. Structural Features and Sulfation Patterns of Marine-Derived Anticoagulants

Marine Source	Structural Characteristics	Structure–Activity Relationship	Ref.
Brown algae	Fucose-rich polysaccharides with predominant 2-O and 3-O sulfation	Strong anticoagulant activity through interaction with coagulation factors; sulfate density enhances electrostatic binding to thrombin and FXa	(García-Zamora et al., 2025; George et al., 2024)
Green algae	Galactose/arabinose backbone; sulfation at C-2, C-3, O-4, O-6; variable molecular weight	Anticoagulant activity depends on molecular weight and sulfate positioning; determines intrinsic versus common pathway modulation	(Peipei et al., 2024; Qin et al., 2025; Yao et al., 2025)
Red algae	Sulfation mainly on galactose residues (e.g., 2,3-disulfated α-D-galactose); branching variability	Activity strongly linked to sulfation degree and molecular mass; higher sulfation correlates with stronger thrombin inhibition	(Ismail & Amer, 2020; Sampaio et al., 2020; Yu et al., 2021)
Cross-species comparison	Variation in sulfation pattern, molecular weight, and branching architecture	Sulfation pattern, chain length, and branching collectively modulate potency, selectivity, and safety profile; minor structural changes may significantly alter bioactivity	(George et al., 2024; Peipei et al., 2024; Qin et al., 2025; Sampaio et al., 2020)

Detailed structural characterization, including sulfate mapping and molecular weight profiling, is essential to optimize anticoagulant efficacy and minimize adverse effects, as even small variations in sulfation or depolymerization can markedly alter biological activity (Qin et al., 2025). Table 1 confirms that sulfate positioning (2-O, 3-O, 6-O), branching architecture, and chain length act synergistically to determine potency and selectivity. Cross-species comparison reveals that even minor alterations in sulfation topology may shift activity from thrombin-dominant inhibition toward intrinsic pathway modulation, reinforcing the need for precise structural characterization.

Table 2. Emerging Extraction, Purification, and Structural Engineering Strategies

Strategy Category	Technological Approach	Functional Objective	Ref.
Green extraction	Enzyme-assisted, ultrasound-assisted, microwave-assisted, subcritical water extraction	Improve yield, purity, and sustainability while preserving sulfate integrity	(Gao et al., 2020; Moreira et al., 2021; Naseem et al., 2025; J. Sun et al., 2025; Torabi et al., 2024)
Purification	Ion-exchange chromatography, dialysis, membrane ultrafiltration	Isolate highly bioactive fractions and improve reproducibility	(Ferreira et al., 2025; Sichert et al., 2021)
Chemical modification	Depolymerization, oversulfation, carboxymethylation	Increase negative charge density and enhance interaction with coagulation proteins	(Babuty et al., 2025)
Nanotechnology integration	Marine polysaccharide-based nanocarriers (e.g., sodium alginate sulfate-coated Fe3O4 nanoparticles)	Improve delivery efficiency, stability, and recyclability	(C. Li et al., 2020)

Table 2 highlights that extraction and engineering strategies are not merely technical refinements but functional determinants of activity. Green extraction methods preserve sulfate integrity, purification improves reproducibility of bioactive fractions, and chemical modification increases charge density and protease interaction (Babuty et al., 2025; Gao et al., 2020; Torabi et al., 2024).

Thus, production methodology directly influences structural fidelity and, consequently, anticoagulant performance. The integration of green extraction technologies with controlled chemical modification is critical for scalable, reproducible production of high-purity marine anticoagulants (J. Sun et al., 2025; Torabi et al., 2024).

Molecular Mechanisms and Pharmacological Profiles Mechanisms of Action and Molecular Targets

Marine-derived anticoagulants exert their biological effects through both classical and emerging molecular pathways, reflecting a multidimensional pharmacological profile that extends beyond conventional heparin-like activity. The classical mechanism primarily involves SERPIN (serine protease inhibitors)-mediated potentiation, in which sulfated marine polysaccharides enhance the inhibitory activity of endogenous serine protease inhibitors such as antithrombin III (ATIII) and heparin cofactor II (HCII). Through conformational activation of these SERPINs, marine glycans accelerate the neutralization of key coagulation proteases, particularly thrombin (FIIa) and factor Xa (FXa), thereby suppressing fibrin formation and thrombus propagation. This indirect amplification mechanism resembles that of mammalian heparin but often differs in structural determinants, including sulfation pattern, backbone composition, and molecular weight, which may influence selectivity and bleeding risk (Carle et al., 2021; Qin et al., 2023).

Beyond SERPIN-dependent modulation, several marine-derived compounds operate through novel mechanisms that directly target specific coagulation enzymes. Certain peptides and

structurally defined oligosaccharides inhibit intrinsic pathway proteases such as factor XIa (FXIa) or factor XIIa (FXIIa), reducing thrombin generation at earlier stages of the coagulation cascade. Direct enzyme inhibition offers a more targeted strategy, potentially preserving physiological hemostasis while limiting pathological thrombosis. This approach aligns with current efforts in anticoagulant development to uncouple antithrombotic efficacy from excessive bleeding complications (Carle et al., 2021; Qin et al., 2023).

In addition to coagulation factor modulation, marine polysaccharides exhibit immunomodulatory properties that further expand their therapeutic relevance. By regulating cytokine release, attenuating complement activation, and influencing immune cell signaling, these compounds may mitigate thromboinflammatory processes in which coagulation and inflammation are tightly interconnected. The ability to simultaneously modulate coagulation pathways and inflammatory cascades positions marine anticoagulants as multifunctional agents with potential utility in complex disorders such as sepsis, viral infections, and immune-mediated thrombotic conditions (Kondaveeti et al., 2025; Paulose & Chakraborty, 2025) .

Collectively, the coexistence of classical SERPIN-mediated potentiation and novel direct or immunomodulatory mechanisms underscores the pharmacological versatility of marine anticoagulants. This dual mechanistic framework broadens their therapeutic potential, supporting the development of next-generation antithrombotic agents that integrate efficacy, selectivity, and safety within a single molecular platform (Carle et al., 2021; Qin et al., 2023).

Immunomodulatory and Dual Antiviral Effects

Beyond their anticoagulant properties, several marine-derived compounds demonstrate antiviral and immunomodulatory activities, thereby expanding their therapeutic relevance in thromboinflammatory and infectious conditions. Certain sulfated marine polysaccharides have been shown to interfere with viral entry and replication, including viruses such as SARS-CoV-2 and HIV-1 (Abo Elmaaty et al., 2022; Isnawati & Widayati, 2023). Mechanistically, these negatively charged glycans may bind to viral surface proteins or host cell receptors, thereby blocking viral attachment and membrane fusion. In addition, interference with viral proteases or replication-associated enzymes has been reported, suggesting that marine glycans may exert multi-stage antiviral effects. The structural features responsible for anticoagulant activity—particularly high sulfation density and specific glycosidic configurations—also contribute to electrostatic interactions with viral proteins, underscoring a structural convergence between anticoagulant and antiviral mechanisms (Abo Elmaaty et al., 2022; Isnawati & Widayati, 2023).

In parallel, marine polysaccharides exhibit immunomodulatory functions that may mitigate excessive inflammatory responses. Suppression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 has been documented, alongside modulation of key intracellular signaling pathways including NF-κB and MAPK cascades. Through attenuation of these pathways, marine compounds may reduce endothelial activation, cytokine-driven coagulation amplification, and complement-mediated inflammation. Restoration of immune tolerance and regulation of immune cell activity further support their role in dampening hyperinflammatory states. These effects are particularly relevant in disorders characterized by immune–coagulation crosstalk, such as sepsis or viral-associated coagulopathy (Boominathan & Govindaswamy, 2025; J. Zhang, 2025).

The therapeutic implication of these dual properties is significant. In complex clinical scenarios such as COVID-19, where viral infection, systemic inflammation, and hypercoagulability coexist, compounds that combine anticoagulant, antiviral, and immunomodulatory effects may provide synergistic benefits. Rather than targeting coagulation

alone, such multifunctional agents address the broader pathophysiological network driving disease severity (Abo Elmaaty et al., 2022; Isnawati & Widayati, 2023).

The coexistence of anticoagulant and antiviral/immunomodulatory activities confers a unique pharmacological advantage to marine-derived compounds, positioning them as promising candidates for integrated therapeutic strategies in complex thromboinflammatory disorders (Abo Elmaaty et al., 2022; J. Zhang, 2025).

Role of Heparin Cofactor II and Antithrombin III

The anticoagulant activity of many marine sulfated polysaccharides is mediated through activation of endogenous serine protease inhibitors, particularly antithrombin III (ATIII) and heparin cofactor II (HCII). Upon binding to these SERPINs, marine glycans induce conformational changes that accelerate the inhibition of thrombin (FIIa) and factor Xa (FXa), ultimately prolonging clotting times and suppressing fibrin formation 40 57 66. This mechanism parallels that of heparin but may differ in affinity, selectivity, and kinetic profile depending on structural characteristics (Q. Chen et al., 2024; He et al., 2021; Qin et al., 2023)

Structural determinants play a central role in modulating these interactions. The degree of sulfation, position of sulfate groups, monosaccharide composition, and polymer length collectively influence binding affinity to ATIII and HCII (Q. Chen et al., 2024; W. Zhang et al., 2022). Specific sulfation motifs enhance electrostatic interactions with positively charged domains on SERPIN molecules, while excessive depolymerization or suboptimal sulfation patterns may reduce biological efficacy. Thus, fine structural tuning is essential to balance anticoagulant potency with bleeding risk (Rein et al., 2011).

From a clinical perspective, compounds capable of activating both ATIII and HCII pathways may offer enhanced therapeutic efficacy by targeting multiple nodes within the coagulation cascade. Dual SERPIN-dependent activity may provide broader suppression of thrombin generation while maintaining mechanistic specificity. However, the safety profile remains closely linked to structural parameters, reinforcing the need for precise molecular characterization in preclinical development (He et al., 2021; Qin et al., 2023).

A comprehensive understanding of SERPIN interactions, particularly those involving ATIII and HCII, is critical for rational design of marine anticoagulants and for predicting their pharmacodynamic and clinical behavior (He et al., 2021; Qin et al., 2023). As illustrated in **Fig. 1**, marine-derived anticoagulants exert antithrombotic effects through multiple coordinated mechanisms, including SERPIN activation, intrinsic pathway inhibition, and immuno–antiviral modulation

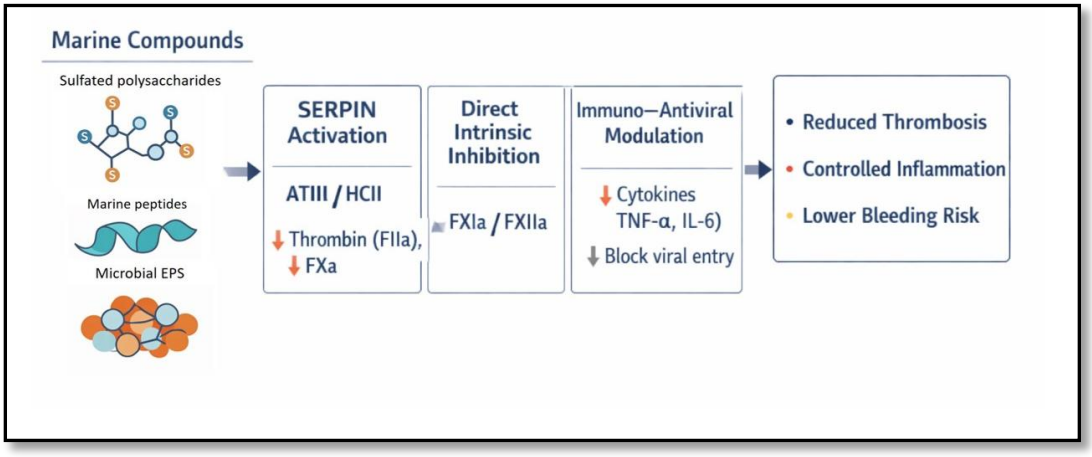

Figure 1. Marine-derived anticoagulants: multidimensional mechanisms.
Schematic representation of multidimensional anticoagulant mechanisms.
Abbreviations: ATIII, antithrombin III; HCII, heparin cofactor II; FIIa, thrombin; FXa, factor Xa.

Clinical Translation, Research Gaps, and Future Directions

The development of marine-derived anticoagulants remains largely within the preclinical and early translational stages. Most candidate compounds, particularly sulfated polysaccharides such as fucoidan, ulvan, and marine glycosaminoglycans, have demonstrated consistent anticoagulant activity through potentiation of antithrombin and heparin cofactor II, as well as modulation of intrinsic pathway factors in both in vitro and in vivo thrombosis models. Anticoagulant efficacy is commonly evaluated using coagulation assays including Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT), together with animal thrombosis models such as zebrafish and small mammals (Kitano et al., 2025; Krishnaswamy et al., 2025; Mao et al., 2021).However, most marine-derived candidates have not yet progressed to advanced phase clinical trials.

Early translational strategies primarily focus on structural optimization, including modulation of molecular weight, sulfation pattern, and selective chemical modification to enhance anticoagulant potency while minimizing bleeding risk (Dwivedi & Pomin, 2020; K. Li et al., 2025; Z.-D. Liu et al., 2025). In addition to anticoagulant effects, several marine polysaccharides exhibit anti-inflammatory and endothelial-protective properties, supporting their potential role in thromboinflammatory conditions.

A major barrier to clinical translation is structural heterogeneity and batch-to-batch variability, which complicate standardization and reproducibility of biological activity (S. Li et al., 2025; Salama et al., 2022; M. Sun et al., 2025; Tripathi et al., 2025; Wu et al., 2025). The intrinsic complexity of marine polysaccharides, including variations in monosaccharide composition and molecular weight distribution, necessitates advanced analytical characterization to ensure quality control, safety, and regulatory compliance.

Pharmacokinetic limitations also represent a significant challenge. High-molecular-weight polysaccharides generally exhibit low oral bioavailability due to limited aqueous solubility, enzymatic degradation, efflux transporter activity, and first-pass metabolism (Bhardwaj et al., 2024; Kim et al., 2023; Onoue et al., 2025; Salman & Alhammid, 2024). To address these barriers, formulation strategies involving nanoparticles, alginate-based nanogels, fucoidan–chitosan complexes, and Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) are being investigated to improve stability and systemic absorption (M. Liu et al., 2022; Mao et al., 2021; Pozharitskaya et al., 2020). Despite promising preclinical findings, most of these advanced delivery platforms remain at the experimental stage (Jim et al., 2025; Wathoni et al., 2024).

Sustainable sourcing and environmental constraints further influence large-scale development. Harvesting seaweed and other marine organisms requires ecological consideration and resource management. Consequently, green extraction technologies, integrated biorefinery approaches, and exploration of marine microorganisms as controlled and scalable sources have become active research priorities (Bahrami et al., 2025; Herrera Barragán et al., 2022; Parmar et al., 2025; Schmidt & Lin, 2022; J. Sun et al., 2025).

Future innovation pathways include selective targeting of intrinsic pathway factors such as factor XIa and factor XIIa, as well as multifunctional strategies integrating antithrombotic and anti-inflammatory mechanisms. Integration of genomics, synthetic biology, and high-throughput screening platforms may accelerate identification of structurally defined candidates with improved selectivity and safety profiles (Parmar et al., 2025; Rajakumar et al., 2024).

Overall, marine-derived anticoagulant research is currently positioned at the mechanistic exploration and preclinical optimization stage. Progression toward advanced clinical trials will require rigorous structural standardization, comprehensive pharmacokinetic validation, stable and scalable formulation development, and carefully designed early-phase clinical studies emphasizing safety and mechanistic differentiation (Dwivedi & Pomin, 2020; K. Li et al., 2025; Z.-D. Liu et al., 2025). Multidisciplinary integration across structural chemistry, pharmacology, marine biotechnology, and drug delivery science will be essential to achieve successful clinical translation.

CONCLUSION

Marine-derived anticoagulants have advanced significantly from 2020 to 2025, with diverse marine sources yielding structurally unique compounds that act through both classical and novel mechanisms. Progress in extraction technologies, chemical modification, and nanodelivery systems continues to enhance their therapeutic potential and translational feasibility. However, persistent challenges including structural heterogeneity, pharmacokinetic limitations, sustainable sourcing constraints, and regulatory hurdles must be systematically addressed through interdisciplinary research, green technological innovation, and well-designed clinical trials. The future of marine anticoagulant research depends on integrating synthetic biology, advanced analytical platforms, and personalized medicine approaches to develop safe, effective, and sustainable therapies for thrombotic and related disorders.

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