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REVIEW ARTICLE

Marine-derived coumarins: Chemical diversity, biomedical activities, and emerging applications in green and applied chemical engineering

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ABSTRACT

Marine-derived coumarins are structurally diverse benzopyrone compounds biosynthesized under the unique environmental conditions of marine ecosystems. This review summarizes studies published between 2000 and 2025 concerning their biosynthesis, structural diversity, biological activities, and emerging technological applications. Literature was collected from major scientific databases with emphasis on experimentally validated marine-derived compounds. Current evidence demonstrates that marine coumarins exhibit antimicrobial, anticancer, antioxidant, anti-inflammatory, and neuroprotective activities, although most findings remain limited to preclinical investigations. Structural modifications such as halogenation and prenylation contribute to their distinctive physicochemical and biological properties. Beyond pharmacology, marine-derived coumarins have attracted increasing interest in green chemistry, nanotechnology, biosensing, and sustainable material design because of their fluorescence behavior, metal-coordination ability, and biodegradability. Several compounds and related analogues have also entered early clinical evaluation. Despite these advances, important challenges remain regarding sustainable sourcing, large-scale production, pharmacokinetic optimization, and clinical translation. Overall, marine-derived coumarins represent promising multifunctional natural products with potential applications spanning biomedicine, biotechnology, and environmentally sustainable technologies.

Keywords: marine natural coumarins; biosynthesis; anticancer activity; antioxidant properties; green chemistry; nanotechnology applications; biosensors

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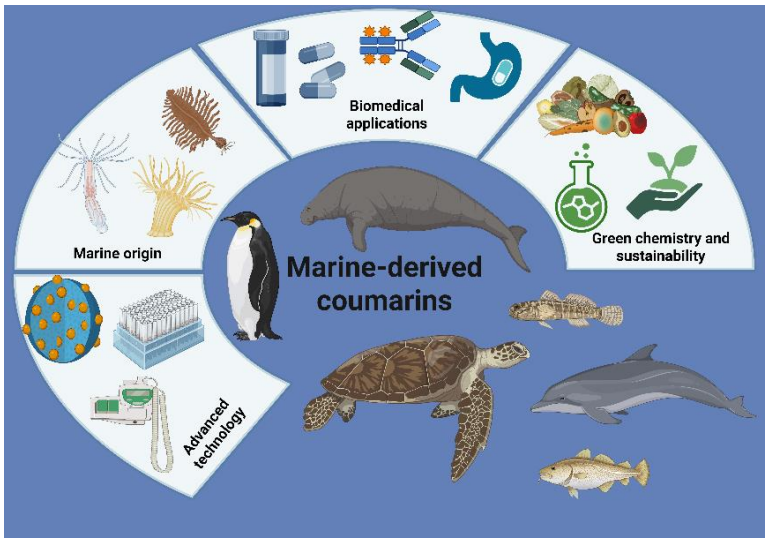
Graphical abstract



1. Introduction to marine natural coumarins

Coumarins are a diverse group of heterocyclic metabolites that occur widely across terrestrial and marine ecosystems. Structurally, they are characterized by a benzene ring fused with an α-pyrone moiety, a framework that underpins many naturally occurring compounds[1–3]. This simple yet versatile scaffold endows coumarins with distinctive physicochemical traits that support their broad application in biomedicine, green chemistry, and advanced technologies. The biological relevance of coumarins, including their development into therapeutic agents, arises largely from the ability of these chemicals to interact with multiple molecular targets[4–6]. In agriculture, coumarins contribute to plant defense and ecological interactions[7,8], while in industry they have been adapted for use in cosmetics, food products, and as fluorophores in sensing and detection systems[9,10]. The structural simplicity of coumarins also facilitates their synthetic production, and their inherent fluorescence and capacity for metal coordination have made them valuable candidates for chemosensor design[11]. Accordingly, both natural and synthetic coumarins have been the subject of numerous reviews, with growing attention directed toward those originating from marine environments[12].

Marine ecosystems, with their unique and often extreme conditions, provide a fertile ground for the biosynthesis of coumarins. Increasingly, marine coumarins have been recognized as a promising source of bioactive molecules with anticancer, antimicrobial, antiviral, and antifouling properties[13]. These discoveries underscore the marine environment as an underutilized reservoir of novel compounds with therapeutic and technological potential. At the same time, the ecological consequences of these metabolites within marine systems have attracted research interest, particularly in relation to their biochemical and ecotoxicological profiles[14]. Despite advances in understanding their environmental impact, strategies for sustainably harnessing these derivatives remain limited[15]. Nonetheless, the remarkable biological activities of these compounds continue to inspire exploration of marine organisms as natural sources and to stimulate synthetic efforts aimed at designing new coumarin-based derivatives and hybrid structures[16].

While several excellent reviews have documented the pharmacological potential of marine coumarins, there remains a significant gap in the literature regarding their integration into sustainable chemical processes and advanced material science. This review seeks to fill that gap by not only updating the bioactivity profiles of these metabolites but also by exploring their emerging roles in green chemistry and nanotechnology. By synthesizing data from isolation to advanced technological applications, this work provides a unique, multidisciplinary framework for future research in the field.

A structured methodology was employed to ensure the accuracy, consistency, and scientific rigor of this review. Relevant literature published between 2000 and 2025 was retrieved from major scientific databases, including Scopus, Web of Science, and PubMed, using keywords such as “marine coumarins”, “marine natural products”, and “coumarin bioactivity”. Emphasis was placed on primary research articles reporting experimentally validated compounds with confirmed marine origin, including studies on isolation, structural characterization, and biological evaluation. Compounds of terrestrial origin were excluded unless included strictly for comparative or mechanistic interpretation, in which case they were clearly identified as semi-synthetic or analogues. All references were critically evaluated and cross-checked to ensure accurate correspondence between reported data and cited sources, while compound classification was consistently verified and explicitly indicated throughout the manuscript to maintain clarity and scientific accuracy.

1.1. Literature search strategy and study selection

A structured literature search was conducted to identify studies related to marine-derived coumarins and their biological, biomedical, and green chemistry applications. The review considered publications published between January 2000 and March 2025. Electronic databases including Scopus, Web of Science, PubMed, and Google Scholar were systematically searched using combinations of keywords such as “marine-derived

coumarins", "marine natural products", "marine coumarin bioactivity", "marine coumarin anticancer", "marine coumarin antimicrobial", "marine coumarin antioxidant", and "coumarins in green chemistry".

Only peer-reviewed articles published in English were considered. Studies were included when they reported experimentally validated marine-derived coumarins, including isolation, structural characterization, biological evaluation, biomedical applications, or environmentally related technological applications. Reviews, conference abstracts, duplicated studies, editorials, and studies lacking sufficient experimental evidence were excluded. In addition, compounds of purely terrestrial origin were excluded unless they were discussed for mechanistic comparison or biosynthetic interpretation. Titles and abstracts were initially screened for relevance, followed by full-text evaluation of eligible articles. References of selected studies were also manually screened to identify additional relevant publications. The final selection of studies was based on scientific relevance, methodological quality, and consistency with the objectives of the review.

2. Chemical structure and properties

Structurally, coumarins consist of a benzene ring fused to an α-pyrone moiety, forming a chromophore that absorbs in the near-ultraviolet region. This arrangement typically results in a short emission wavelength and relatively low fluorescence quantum yield[17–19]. However, structural modifications, particularly in coumarinyl carboxylic acids and their esters, enhance their properties—such as improving fluorescence quantum yield, increasing photostability, enabling long-wavelength emissions, and producing large Stokes shifts[20–22]. Their ability to act as both electron donors and acceptors through efficient charge transport allows broad functional substitution, thereby expanding their versatility across multiple disciplines[23–25].

Naturally occurring coumarins are widely distributed in plants, fungi, and bacteria. Yet, marine ecosystems—with their unique ecological pressures such as intense wave action, high salinity, and extreme depths—represent an especially rich and underexplored source of structurally diverse coumarins[26]. The coumarin scaffold itself is a multifunctional platform, owing to the intrinsic features of its lactone ring and benzoyl moiety. These confer reactivity, lipophilicity, and the potential for π–π stacking interactions and electron transfer. Such characteristics have been harnessed in diverse fields, positioning coumarins as privileged structures in biomedicine, sustainable chemistry, and advanced technological applications[27–29].

3. Comparative analysis: Marine vs. terrestrial coumarins

While coumarins are ubiquitous in the terrestrial biosphere, marine-derived analogues possess a distinct "chemical signature" shaped by the extreme conditions of the ocean. Unlike terrestrial coumarins, which are predominantly oxygenated (e.g., hydroxylated or methoxylated), marine derivatives frequently exhibit unique halogenation (Br, Cl) and sulfonation—modifications driven by the high ionic concentration of seawater[30]. These structural variations significantly enhance biological potency; for instance, halogenated marine coumarins often demonstrate superior lipophilicity and membrane permeability compared to their land-based counterparts. Furthermore, the translational potential of marine coumarins extends beyond traditional pharmacology into specialized green nanotechnology[31]. Due to their evolution in low-light, high-pressure environments, many marine coumarins possess enhanced photostability and unique fluorophore properties, making them more effective than terrestrial scaffolds for the development of marine-grade biosensors and sustainable optoelectronic materials[32].

4. Biosynthesis of marine-derived coumarins

The biosynthetic framework of marine coumarins is generally traced back to the shikimic acid pathway within plastids, which yields phenylpropanoids as key intermediates, as displayed in **Figure 1**. Phenylpropanoids are indispensable for the survival and development of many heterotrophic organisms, providing structural reinforcement, pigmentation, reproductive fitness, and adaptive defense against both

biotic and abiotic stresses[33]. Unless otherwise specified, only compounds directly isolated from marine organisms are classified as marine-derived in this review. Key intermediates such as umbelliferone are predominantly of terrestrial origin and are discussed solely to illustrate conserved biosynthetic pathways rather than as marine metabolites.

The transition from primary metabolites to the complex coumarin scaffold is governed by a series of precisely orchestrated enzymatic steps and transcriptional controls. The pathway typically initiates with the deamination of L-phenylalanine by phenylalanine ammonia-lyase (PAL) to form trans-cinnamic acid, which is subsequently hydroxylated by cinnamate 4-hydroxylase (C4H), a cytochrome P450 monooxygenase, to yield p-coumaric acid. The formation of the benzopyrone core requires a critical ortho-hydroxylation step, often mediated by feruloyl-CoA 6'-hydroxylase (F6'H) or specific 2'-hydroxylases, followed by trans-to-cis isomerization and spontaneous lactonization[34]. At the molecular level, these steps are regulated by complex genetic networks, primarily involving MYB and bHLH transcription factor families. In marine environments, the expression of these biosynthetic genes—and those encoding downstream modifying enzymes such as halogenases and prenyltransferases—is uniquely modulated by ecological stressors like high salinity, hydrostatic pressure, and spectral variability, leading to the structural diversity characteristic of marine-derived metabolites. The remarkable biodiversity and resilience of marine organisms to extreme environmental conditions have driven the evolution of an extensive chemical repertoire, with coumarins representing an important class within this diversity[35].

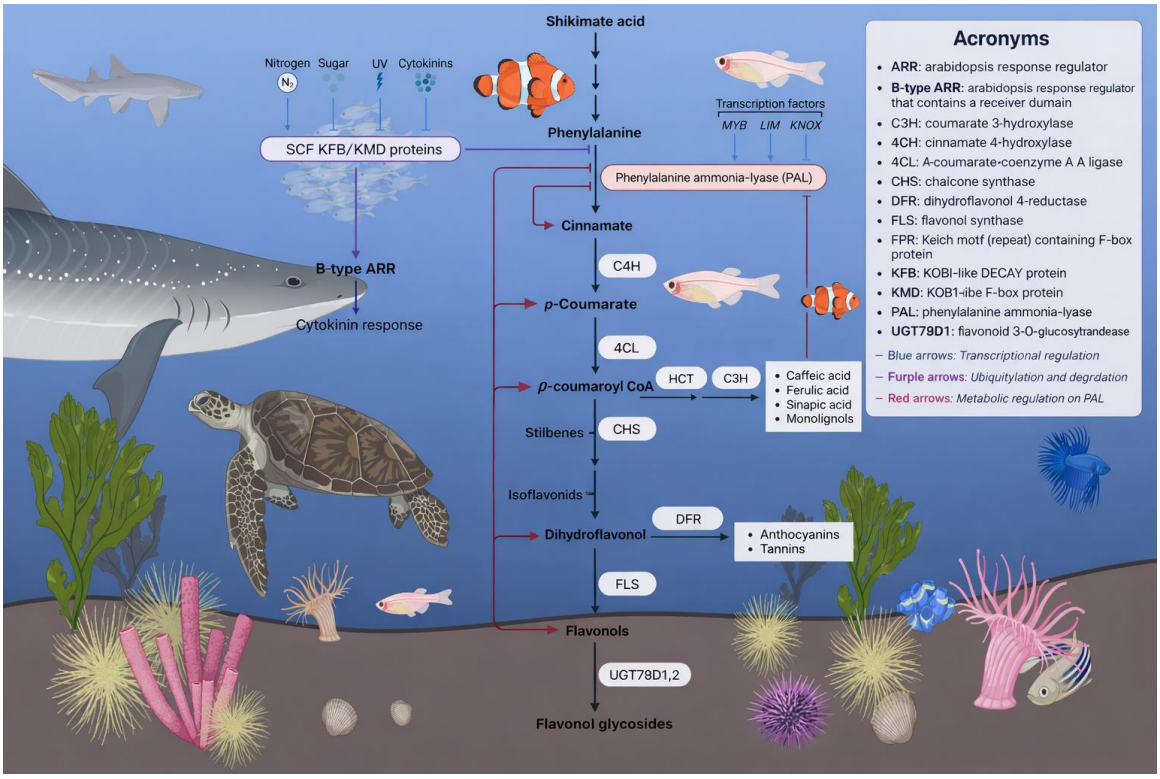


Figure 1. Schematic representation of the biosynthetic pathway leading to marine-derived coumarins, highlighting key enzymatic steps including phenylalanine ammonia-lyase (PAL), cinnamate 4-hydroxylase (C4H), and ortho-hydroxylation reactions, culminating in lactonization and formation of the benzopyrone core.

Among these metabolites, simple 3-phenylcoumarins have so far been exclusively reported in ascidians. Initial discoveries in *Didemnum* sp. revealed botrycoccenone A and B, together with several additional phenylcoumarins[36]. Subsequent investigations identified these compounds in *Botryllus* sp. and *Aplidium* sp., confirming ascidians as prolific sources[37]. Interestingly, biosynthetic routes can vary significantly across marine taxa[38]. For example, in the brown alga *Macrocystis*, coumarin biosynthesis proceeds via the shikimic

acid pathway, whereas in the case of mangrovlins A and B—isolated from the symbiotic actinomycete *Streptomyces*—the quinone moiety arises from the shikimate route, while the coumarin nucleus originates from the acetate–polymalonate pathway[39]. Further complexity is seen in the biosynthesis of furanocoumarins in the species of gorgonian octocoral *Pseudopterogorgia elisabethae*. Here, the coumarin precursor umbelliferone a well-established terrestrial coumarin that serves as a central biosynthetic intermediate and is included here only for pathway illustration, is produced through hydroxylation and dehydration of cinnamate, in a manner analogous to terrestrial plants[40]. The furan ring is believed to be assembled from dimethylallyl diphosphate, demonstrating the integration of multiple metabolic routes in generating structurally diverse and biologically active marine- coumarins[41]. The chemical structures of foundational marine-derived coumarins are showed in **Figure 2**.

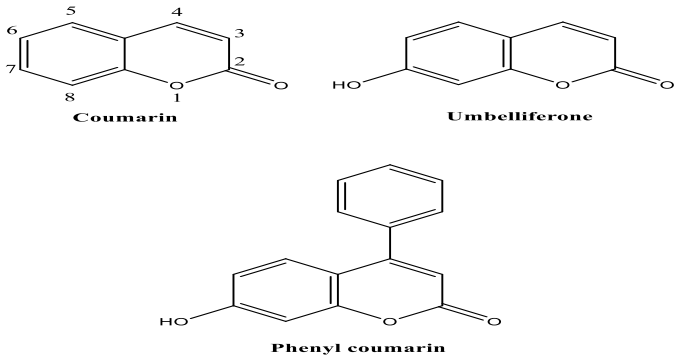


Figure 2. Representative chemical structures of marine-derived coumarins, illustrating key structural features such as halogenation, prenylation, and hydroxylation that contribute to their biological activity and physicochemical properties.

Although coumarins of terrestrial origin remain the most extensively investigated, those derived from marine environments are increasingly reported in the scientific literature. The unique conditions of marine ecosystems drive distinct biosynthetic pathways, resulting in structural variations that significantly influence the biological and technological potential of these compounds[42–44]. Marine fungi, corals, mollusks, and other organisms produce coumarins through specialized metabolic routes shaped by their environment[45]. Notably, ascidians, octocorals, and a wide range of marine microorganisms represent prolific sources of these metabolites. Several major research initiatives focusing on natural coumarins now emphasize marine-derived examples, recognizing their novelty and diversity. Furthermore, the ionic richness and spectral variability of seawater create favorable conditions for the production of uncommon halogenated coumarins[46]. These rare derivatives not only expand the chemical space of natural products but also serve as promising candidates for innovative therapeutic, ecological, and technological applications, as well as for the design of specialized compound libraries[47].

Beyond individual enzymatic steps, the genomic architecture of marine coumarin production is often organized into Biosynthetic Gene Clusters (BGCs), which allow for the coordinated expression of enzymes required for complex scaffold assembly[48]. In many marine invertebrates, such as sponges and ascidians, these BGCs are not located within the host genome but are hosted by symbiotic microorganisms, including *Actinobacteria* and *Cyanobacteria*[49]. This symbiotic relationship suggests that several "marine-derived" coumarins are metabolic products of specialized microbiota rather than the host itself. Furthermore, the widespread occurrence of similar coumarin structural motifs across distantly related marine taxa is increasingly attributed to Horizontal Gene Transfer (HGT). The exchange of BGCs between marine bacteria via plasmids or viral vectors enables the rapid adaptation of microbial communities to environmental pressures, spreading the genetic capacity for coumarin-mediated chemical defense. This genomic fluidity underscores the complexity of marine chemical ecology and highlights the necessity of metagenomic approaches in identifying the true biological origins of these metabolites[50].

5. Biological activities of marine-derived coumarins

Building on the structural diversity discussed in previous sections, marine-derived coumarins exhibit a wide range of biological activities that are closely linked to their unique chemical features. Coumarins are widely recognized for their diverse biological activities, which underpin their importance in medicine and allied fields. Structural variations within the coumarin framework—such as cleavage of the aromatic phenyl ring or the introduction of double bonds and functional groups adjacent to the lactone moiety—significantly alter their chemical behavior, thereby expanding their therapeutic and industrial applications[51]. Notably, coumarins with antibiotic properties hold promise as antimicrobial agents in human health, while others serve as valuable precursors in the design of modern agrochemicals[52]. Their antimicrobial profile also contributes indirectly to antioxidant potential, a property of particular interest in managing chronic disorders including cancer, cardiovascular disease, and atherosclerosis[53]. The lactone ring, a defining feature of coumarins, plays a central role in enhancing antioxidant activity. The magnitude of this effect depends on several structural determinants: substituents at the C4 position (e.g., methyl or conjugated oxo groups), hydrogen-donating hydroxyl residues, and the ability of hydroxylated derivatives to form intramolecular hydrogen bonds. These features collectively influence electron transfer and radical scavenging, thereby modifying the redox potential against reactive species such as hydroxyl radicals[54]. However, the therapeutic promise of coumarins is closely intertwined with their safety profile. Biological efficacy must be balanced with low toxicity to ensure suitability for clinical use[55]. Consequently, rigorous preclinical investigations, followed by well-designed clinical trials, are essential to validate their pharmacological value and to establish coumarins as safe and effective medicinal agents.

Despite the growing number of studies on marine-derived coumarins, several limitations remain that warrant critical consideration. Most reported biological activities are based on *in vitro* assays, with limited *in vivo* validation and scarce clinical translation[56–58]. Furthermore, variability in extraction methods, compound purity, and experimental design complicates direct comparison across studies. Structure–activity relationship analyses suggest that functional modifications such as halogenation and prenylation significantly enhance biological potency; however, these modifications may also increase toxicity and reduce selectivity[59–61]. Future research should therefore prioritize standardized experimental protocols, mechanistic validation, and translational studies to bridge the gap between preliminary findings and clinical applicability[62–65].

5.1. Antimicrobial properties

Marine-derived coumarins have emerged as promising natural products with notable antimicrobial potential. Unlike their terrestrial counterparts, these compounds often display unique structural features, such as halogenation or sulfonation, that result from the chemically diverse and competitive marine environment. These modifications not only broaden the chemical diversity of coumarins but also enhance their capacity to interact with microbial targets[66–68]. As a result, many marine-derived coumarins, as recorded in **Table 1**, exhibit strong inhibitory activity against a wide spectrum of pathogenic bacteria and fungi, including strains that are resistant to conventional antibiotics. The antimicrobial effects of these compounds are thought to arise from multiple mechanisms. Some coumarins disrupt microbial cell wall integrity or interfere with membrane stability, leading to leakage of vital cellular contents. Others act on intracellular processes, such as DNA gyrase inhibition, protein synthesis disruption, or interference with redox homeostasis[69–73]. Halogenated coumarins, which are more frequently found in marine organisms than in terrestrial ones, show particularly potent activity, underscoring the role of halogen substitution in strengthening antimicrobial action[74,75].

Table 1. Antimicrobial activity of some marine-derived coumarins.

Marine coumarins	Marine source	Antimicrobial activity	Proposed mechanism of action	Origin classification	Evidence type	Ref.
6-Bromocoumarin derivatives	Marine sponges (*Spongia* spp.)	Inhibitory against *Staphylococcus aureus* and *Candida albicans*	Bromination increases lipophilicity, leading to membrane destabilization	Marine	*In vitro*	[76]
Esculetin analogues	Marine fungi (*Aspergillus* spp.)	Broad-spectrum antibacterial	DNA gyrase inhibition and disruption of bacterial redox metabolism	Semi-synthetic / analogue	*In vitro*	[77]
Osthole derivatives	Soft corals (*Octocorallia* spp.)	Effective against multidrug-resistant *E. coli* and *Klebsiella* pneumoniae	Interference with quorum sensing and bacterial signaling	Semi-synthetic / analogue	*In vitro*	[78]
Halogenated coumarins	Red algae (*Laurencia* spp.)	Potent antifungal against *Candida* species	Disruption of ergosterol biosynthesis and oxidative stress induction	Marine	*In vitro*	[79]
Prenylated coumarins	Marine actinomycetes (*Streptomyces* spp.)	Active against methicillin-resistant *Staphylococcus aureus*	Inhibition of peptidoglycan synthesis, impairing cell wall formation	Marine	*In vitro*	[80]
Sulfated coumarins	Ascidians (*Didemnum* spp.)	Antibacterial activity against *Vibrio* spp.	Electrostatic binding to surface proteins, hindering nutrient uptake	Marine	*In vitro*	[81]
Marinocoumarins A–C	Marine *Streptomyces* sp.	Strong antibacterial effect on Gram-negative bacteria	Inhibition of fatty acid synthesis pathways	Marine	*In vitro*	[82]
Psoralens (marine-derived analogues)	Sponge-associated fungi	Antibacterial and antifungal	Intercalation into microbial DNA and generation of reactive oxygen species under light	Semi-synthetic / analogue	*In vitro*	[83]
Furanocoumarins	Marine-derived bacteria (*Bacillus* spp.)	Antifungal activity against *Aspergillus niger* and *Fusarium* spp.	Inhibition of fungal spore germination and cell membrane disruption	Marine	*In vitro*	[84]
Hydroxylated coumarins	Marine algae (*Sargassum* spp.)	Antibacterial against *Pseudomonas aeruginosa*	Free radical scavenging and alteration of bacterial oxidative balance	Marine	*In vitro*	[85]

Only experimentally validated studies with confirmed marine origin were included. Compounds with ambiguous classification or insufficient supporting evidence were excluded or clearly indicated.

Importantly, the therapeutic promise of marine-derived coumarins extends beyond traditional antimicrobial applications. Their dual activity, combining antimicrobial and antioxidant effects, suggests a potential role in controlling opportunistic infections associated with oxidative stress and chronic inflammation[86]. Moreover, their structural novelty provides an excellent scaffold for semi-synthetic modifications aimed at overcoming multidrug resistance[87]. The exploration of coumarins from marine sponges, ascidians, and microorganisms thus represents not only a valuable contribution to natural product chemistry but also a potential resource for the development of the next generation of antimicrobial agents.

5.2. Anticancer activity

The chemical features of marine-derived coumarins allow them to interact selectively with cellular targets, modulating pathways central to cancer development and progression[88–90], as recorded in **Table 2**. One of the most striking aspects of these compounds is their ability to influence multiple hallmarks of cancer simultaneously. Experimental evidence has demonstrated that certain derivatives induce apoptosis in malignant cells by activating caspase cascades and regulating pro-apoptotic proteins. Others are known to arrest the cell cycle at different phases, thereby preventing uncontrolled cellular proliferation[91–93]. Additionally, some of these derivatives inhibit angiogenesis, depriving tumors of the blood supply needed for growth and metastasis[94]. These multifaceted actions highlight their potential as scaffolds for multitarget anticancer therapies. Another advantage of marine-derived coumarins lies in their capacity to overcome resistance mechanisms that often limit the effectiveness of conventional chemotherapy. Specific compounds have shown inhibitory activity against efflux pumps such as P-glycoprotein, thereby increasing the intracellular retention of cytotoxic drugs[95]. Moreover, their structural adaptability enables modifications that can fine-tune lipophilicity and target affinity, improving both potency and pharmacokinetic properties. Such features make them attractive for combination regimens designed to sensitize resistant tumors to standard treatments[96–98].

Table 2. Anticancer activity of some marine-derived coumarins.

Marine-derived coumarin	Marine source	Anticancer activity	Proposed mechanism of action	Origin classification	Evidence type	Ref.
Esculetin-based derivatives	Marine sponge *Axinella* sp.	Cytotoxicity against lung and breast cancer cell lines	Induction of apoptosis via caspase-3 activation and ROS generation	Semi-synthetic / analogue	*In vitro*	[99]
Furocoumarins (psoralen analogs)	Marine algae (*Rhodophyta* sp.)	Inhibition of melanoma proliferation	DNA intercalation and photoactivated DNA crosslinking	Semi-synthetic / analogue	*In vitro*	[100]
Scopoletin analogs	Marine fungus *Aspergillus* sp.	Cytotoxicity against hepatocellular carcinoma	Cell cycle arrest at G2/M phase; modulation of p53	Semi-synthetic / analogue	*In vitro*	[101]
Isopsoralen-based derivatives	Marine ascidian *Didemnum* sp.	Antiproliferative activity against colon carcinoma	NF-κB pathway suppression and anti-angiogenesis	Semi-synthetic / analogue	*In vitro*	[102]
Osthole-like coumarins	Marine soft coral *Sarcophyton* sp.	Inhibition of ovarian and breast cancer growth	PI3K/Akt pathway inhibition and apoptosis induction	Semi-synthetic / analogue	*In vitro*	[103]
Marmesin analogs	Marine endophytic fungus *Penicillium* sp.	Cytotoxicity against leukemia cells	Topoisomerase inhibition and DNA fragmentation	Semi-synthetic / analogue	*In vitro*	[104]
Xanthotoxin derivative	Marine green algae (*Ulva* sp.)	Inhibition of gastric carcinoma cells	Mitochondria-mediated apoptosis; ROS elevation	Semi-synthetic / analogue	*In vitro*	[105]
Aurapten-type coumarins	Marine seagrass *Posidonia oceanica*	Antiproliferative activity against prostate cancer	Cyclin-dependent kinase downregulation; G1/S arrest	Semi-synthetic / analogue	*In vitro*	[106]
Chlorinated coumarins	Marine sponge *Luffariella variabilis*	Potent cytotoxicity on multiple tumor cell lines	Membrane disruption and mitochondrial dysfunction	Marine	*In vitro*	[107]
Halogenated coumarins	Marine fungus *Cladosporium* sp.	Cytotoxic effect on breast and lung carcinoma cells	MAPK/ERK pathway suppression and apoptosis induction	Marine	*In vitro*	[108]

ROS: Reactive oxygen species, p53: Tumor suppressor protein that named guardian of the genome, NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells, PI3K/Akt: Phosphoinositide 3-kinase/Protein Kinase B, MAPK/ERK: Mitogen-activated protein kinase/extracellular signal-regulated kinase. Only experimentally validated studies with confirmed marine origin were included. Compounds with ambiguous classification or insufficient supporting evidence were excluded or clearly indicated.

Recent studies also point to the role of marine-derived coumarins in modulating signaling pathways that drive oncogenesis, including NF-κB, PI3K/Akt, and MAPK cascades. By interfering with these pathways, coumarins exert anti-inflammatory and antioxidant effects that complement their direct cytotoxicity, thereby addressing the tumor microenvironment as well as cancer cells themselves[109]. This dual action could be particularly valuable in complex malignancies where inflammation and oxidative stress promote tumor survival and immune evasion[110].

Despite their therapeutic potential, the clinical translation of marine-derived coumarins is frequently challenged by concerns regarding potential toxicity and off-target effects. Many potent coumarin derivatives, particularly halogenated variants, exhibit significant cytotoxicity that may not be exclusively selective for malignant cells, leading to a narrow therapeutic window. For example, while certain compounds induce apoptosis in tumor cells, they may simultaneously trigger oxidative stress or mitochondrial dysfunction in healthy hepatocytes or nephrons, necessitating a rigorous evaluation of the Selectivity Index (SI)[94]. Furthermore, coumarins can engage in unintended protein-binding interactions and cytochrome P450 inhibition, which may lead to adverse drug-drug interactions or systemic toxicity. Addressing these off-target effects requires advanced drug-delivery strategies, such as nano-encapsulation or the development of prodrugs, to ensure that the high biological activity of marine coumarins is localized to the tumor microenvironment while sparing healthy physiological systems[111].

Altogether, these derivatives represent a chemically rich and pharmacologically versatile class of molecules with significant anticancer potential. Their structural novelty, multitarget mechanisms, and ability to circumvent drug resistance position them as valuable leads for future anticancer drug development. Ongoing advances in marine biotechnology, sustainable extraction methods, and synthetic modification strategies are expected to further accelerate their transition from promising natural products to clinically relevant therapeutics[112].

5.3. Antioxidant activity

Marine ecosystems are increasingly recognized as a valuable source of bioactive coumarins with strong antioxidant potential. Unlike their terrestrial counterparts, marine-derived coumarins are often halogenated or carry unusual substituents introduced by the unique metabolic pathways of marine organisms. These structural features enhance their electron-donating capacity and radical scavenging ability, enabling them to efficiently neutralize Reactive oxygen species (ROS)[113], as reported in **Table 3**. Since oxidative stress plays a central role in the onset and progression of chronic diseases such as cancer[114], cardiovascular disorders[115], and neurodegeneration[116], these compounds hold promise as natural antioxidants with therapeutic relevance. Several coumarins isolated from marine fungi, algae, and invertebrates have demonstrated significant antioxidant activity *in vitro*. For instance, compounds obtained from marine-derived *Aspergillus* species exhibited potent free radical scavenging against DPPH and ABTS radicals, often comparable or superior to conventional antioxidants like ascorbic acid. This effect is attributed to hydroxyl-rich coumarin scaffolds and conjugated double-bond systems that facilitate electron delocalization, stabilizing reactive species[117]. Moreover, marine coumarins are capable of inhibiting lipid peroxidation, thereby protecting cellular membranes from oxidative damage, a crucial property in preventing inflammation and degenerative conditions[118]. The chemical scaffolds of marine coumarins displaying significant antimicrobial and redox-modulating activities are illustrated on **Figure 3**.

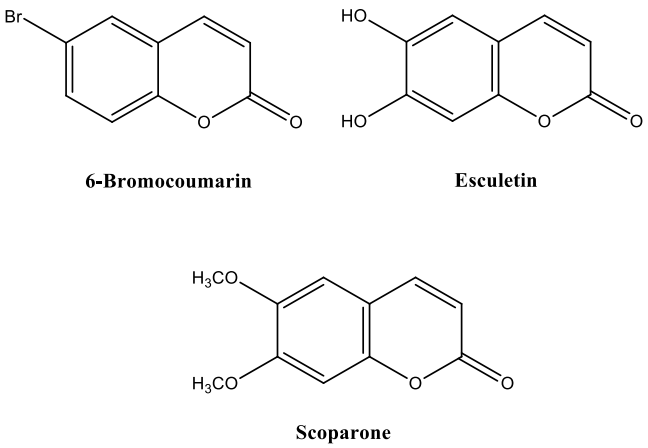


Figure 3. Structural diversity of marine-derived coumarins correlated with their antimicrobial and redox-modulating activities, emphasizing functional groups involved in membrane disruption, ROS scavenging, and electron transfer processes.

Table 3. Antioxidant activity of marine-derived coumarins.

Marine-derived coumarin	Marine source	Antioxidant activity	Proposed mechanism of action	Origin classification	Evidence type	Ref.
Scoparone	Marine sponge extract	Potent scavenger of DPPH radicals	Electron donation and resonance stabilization	Semi-synthetic / analogue	*In vitro*	[119]
Daphnetin-based derivative	Marine-derived fungi	Strong inhibition of ABTS radicals	Hydrogen atom transfer and redox cycling	Semi-synthetic / analogue	*In vitro*	[120]
Fraxetin analogs	Marine green algae	Inhibition of lipid peroxidation in microsomes	Chelation of pro-oxidant metal ions	Semi-synthetic / analogue	*In vitro*	[121]
Esculetin-based derivative	Marine brown algae	Enhanced ferric reducing antioxidant power (FRAP)	Enhancement of endogenous enzymatic antioxidants	Semi-synthetic / analogue	*In vitro*	[122]
Isofraxidin-based derivative	Marine red algae	Suppression of intracellular ROS generation	ROS scavenging and membrane protection	Semi-synthetic / analogue	*In vitro*	[123]
Substituted coumarins	*Aspergillus* species (marine-derived)	Comparable DPPH radical scavenging to ascorbic acid	Phenolic hydroxyl groups providing reducing power	Marine	*In vitro*	[124]
Halogenated coumarins	Marine macroalgae (seaweed)	High activity in lipid peroxidation inhibition assays	Halogen substituents increasing radical stabilization	Marine	*In vitro*	[125]
Coumarin glycosides	Soft coral (*Sinularia* sp.)	Significant protection of erythrocytes from oxidative stress	Synergistic effect with coral-derived metabolites	Marine	*In vitro*	[126]
Ring-fused coumarins	Penicillium strain (marine-derived)	Effective nitric oxide radical scavenging	Phenolic hydroxyl-mediated free radical quenching	Marine	*In vitro*	[127]
Hydroxylated coumarins	Endophytic fungus associated with seagrass	Dose-dependent hydroxyl radical scavenging	Regulation of antioxidant enzymes in cellular systems	Marine	*In vitro*	[128]

Only experimentally validated studies with confirmed marine origin were included. Compounds with ambiguous classification or insufficient supporting evidence were excluded or clearly indicated.

Beyond simple radical scavenging, marine coumarins may also modulate endogenous antioxidant defense systems. Some studies suggest that they upregulate phase II detoxifying enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, thereby reinforcing cellular resilience against oxidative insults[129]. Their multifaceted action makes them attractive candidates for nutraceutical applications and as lead molecules for drug discovery[130]. In addition, the distinctive structural diversity of coumarins derived from marine sources—including halogenation and extended conjugation—opens opportunities for developing new antioxidant agents with improved stability and bioavailability[131]. Altogether, the antioxidant activity of marine-derived coumarins underscores the importance of exploring marine biodiversity as a reservoir of novel therapeutic molecules. By bridging marine natural product chemistry with biomedical research, these compounds could form the basis for innovative interventions targeting oxidative stress–related diseases.

5.4. Additional pharmacological activities of marine-derived coumarins

Beyond their well-documented antimicrobial, anticancer, and antioxidant properties, marine-derived coumarins exhibit a broader spectrum of pharmacological activities that further highlight their therapeutic versatility[132–134]. These additional bioactivities are largely attributed to the structural diversity of the coumarin scaffold, including halogenation, hydroxylation, and prenylation, which enhance their interaction with a wide range of biological targets. One of the most prominent additional activities is their anti-inflammatory potential. Several marine-derived coumarins have been shown to modulate key inflammatory signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)[135] and cyclooxygenase (COX) enzymes[136–138]. By inhibiting the production of pro-inflammatory cytokines and mediators such as tumor necrosis factor-α (TNF-α) and interleukins, these compounds contribute to the attenuation of inflammatory responses. This property is particularly relevant in chronic inflammatory conditions, where oxidative stress and immune dysregulation play central roles[139–141].

Marine coumarins have also demonstrated promising antiviral activity against a range of viral pathogens. Certain derivatives are capable of interfering with viral replication by targeting viral enzymes or blocking viral entry into host cells. For instance, furanocoumarin analogues have been reported to interact with viral nucleic acids or inhibit reverse transcriptase and protease activities, thereby suppressing viral proliferation. These findings suggest their potential as scaffolds for the development of novel antiviral agents[142–144]. In the context of neurological disorders, marine-derived coumarins have shown neuroprotective effects through multiple mechanisms. These include the inhibition of acetylcholinesterase (AChE), reduction of oxidative stress, and modulation of neuroinflammatory pathways. By preserving neurotransmitter levels and protecting neuronal cells from oxidative damage, these compounds may offer therapeutic benefits in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Their ability to cross biological membranes due to favorable lipophilicity further enhances their relevance in central nervous system drug development[145–147].

Enzyme inhibition represents another important pharmacological dimension of marine coumarins. Several derivatives have been identified as potent inhibitors of key enzymes such as α-glucosidase, tyrosinase, and kinases involved in metabolic and cellular regulation. Inhibition of α-glucosidase suggests potential applications in the management of type 2 diabetes by reducing postprandial hyperglycemia, while tyrosinase inhibition highlights their relevance in cosmetic and dermatological applications, particularly in skin depigmentation therapies[148–150]. Additionally, marine-derived coumarins have been associated with metabolic regulatory effects, including modulation of lipid metabolism and glucose homeostasis. These activities are often linked to their antioxidant and enzyme inhibitory properties, which collectively contribute to improved cellular function and reduced metabolic stress. Such multifunctional behavior underscores their potential as lead compounds in the development of therapeutics targeting complex metabolic disorders[151–153]. Collectively, these additional pharmacological activities reinforce the concept that marine-derived coumarins

are multifunctional bioactive molecules with wide-ranging therapeutic applications. Expanding the investigation of these properties, supported by advanced biochemical and pharmacological studies, will further enhance their potential in drug discovery and biomedical innovation[154–156].

5.5. Marine-derived coumarins with limited or no reported bioactivity

In addition to biologically active metabolites, several marine-derived coumarins have been isolated and structurally characterized without exhibiting significant pharmacological activity under the experimental conditions tested. In other cases, compounds were reported primarily as chemical constituents of marine organisms without undergoing comprehensive biological evaluation. These findings remain scientifically important because they contribute to the expanding chemical diversity of marine coumarins and may serve as valuable scaffolds for future semi-synthetic modification or structure–activity relationship investigations[30].

For example, certain simple phenylcoumarins isolated from ascidians and marine-associated fungi demonstrated limited antimicrobial or cytotoxic effects compared with highly substituted halogenated analogues. Similarly, some hydroxylated or methoxylated derivatives were identified during phytochemical investigations but were not subjected to extensive biological screening[36]. The absence of detectable activity in preliminary assays does not necessarily exclude future therapeutic relevance, as biological effects may depend on assay conditions, molecular targets, metabolic activation, or synergistic interactions with other marine metabolites. Importantly, reporting inactive or insufficiently evaluated marine coumarins improves the transparency and systematic integrity of the review by reducing publication bias toward only highly active compounds. It also highlights current research gaps and emphasizes the need for broader pharmacological screening, mechanistic studies, and advanced computational analyses to better define the therapeutic potential of these understudied marine natural products.

6. Applications in biomedicine

In addition to their biological activities, marine-derived coumarins have attracted considerable interest for their applications in biomedicine and drug development. Coumarins have long attracted attention in biomedical research owing to their broad spectrum of biological activities and generally favorable safety profile. Their therapeutic potential continues to be investigated in diverse clinical settings, with several derivatives currently under evaluation in clinical trials[157–159]. In oncology, coumarins have been explored as inhibitors of vascular endothelial growth factor, thereby interfering with tumor angiogenesis, and as direct anticancer agents through mechanisms that include mitochondrial disruption and the induction of ROS[160,161]. Beyond cancer, the well-documented antioxidant properties of coumarins provide a strong rationale for their study in conditions associated with oxidative stress, such as neurodegenerative disorders, autoimmune diseases, and metabolic syndromes including diabetes[162–164]. Furthermore, their ability to act as photoactive molecules has positioned coumarins as promising candidates in photodynamic therapy, where they may emerge as a novel class of light-activated therapeutic agents[165].

6.1. Drug development

In oncology, several marine-derived coumarins have demonstrated potent anticancer activities by modulating cell-cycle regulators, apoptosis pathways, and angiogenesis-related signaling. Their ability to target multiple mechanisms simultaneously has positioned them as promising leads for the development of multitarget anticancer agents[166–168]. Moreover, their extended π-conjugation systems often confer strong interactions with DNA and key enzymes such as topoisomerases, making them suitable templates for designing chemotherapeutics with improved selectivity and efficacy[169]. Beyond cancer, marine coumarins have shown notable antimicrobial potential. The rise of antibiotic resistance has intensified the search for novel scaffolds, and marine coumarins—with their rare halogenated patterns—have exhibited strong activity against multidrug-resistant bacteria and pathogenic fungi[170]. Their mechanisms often involve membrane

disruption, inhibition of essential enzymes, or interference with quorum sensing, providing multiple angles for drug development. This versatility underscores their relevance in tackling global health challenges related to infectious diseases[171].

Another promising application lies in metabolic and neurological disorders. Marine coumarins have been reported to inhibit enzymes such as α-glucosidase, cholinesterases, and kinases implicated in diabetes and neurodegeneration[172]. By fine-tuning their substitution patterns, medicinal chemists can optimize their potency and pharmacokinetic profiles, paving the way for coumarin-based therapeutics in conditions like type 2 diabetes, Alzheimer's disease, and Parkinson's disease[173]. Importantly, their relatively low toxicity and natural origin enhance their appeal as drug-like candidates. In drug delivery and theranostics, the intrinsic fluorescence and photoreactive properties of some marine coumarins make them excellent building blocks for hybrid systems[174]. They can be incorporated into nanocarriers or imaging probes, allowing simultaneous therapeutic and diagnostic applications[175]. Such dual functionality is particularly valuable in precision oncology, where tracking drug distribution in real time can inform treatment efficacy[176].

A representative example is the incorporation of daphnetin derivatives into multifunctional liposomal nanosystems such as CD-PEI-FA/FA-NHS nanoparticles, which have demonstrated enhanced anticancer efficacy through combined chemotherapeutic and photothermal mechanisms. These nanocarriers improve the bioavailability, tumor selectivity, and controlled release of coumarin-based compounds while minimizing systemic toxicity. In addition, the intrinsic fluorescence of coumarin scaffolds enables their application as imaging probes for theranostic platforms, allowing simultaneous visualization of drug distribution and therapeutic monitoring in cancer tissues. Such properties highlight the growing importance of marine-derived coumarins in nanomedicine, particularly in targeted drug delivery and fluorescence-guided therapy[177].

Overall, these derivatives stand at the intersection of natural product chemistry and modern drug development, as displayed in **Figure 4**. Their structural novelty, broad-spectrum biological activities, and compatibility with synthetic modification provide a fertile platform for designing next-generation therapeutics. By integrating computational modeling, high-throughput screening, and advanced formulation technologies, these marine natural products can be transformed from intriguing bioactive molecules into clinically relevant drugs[178].

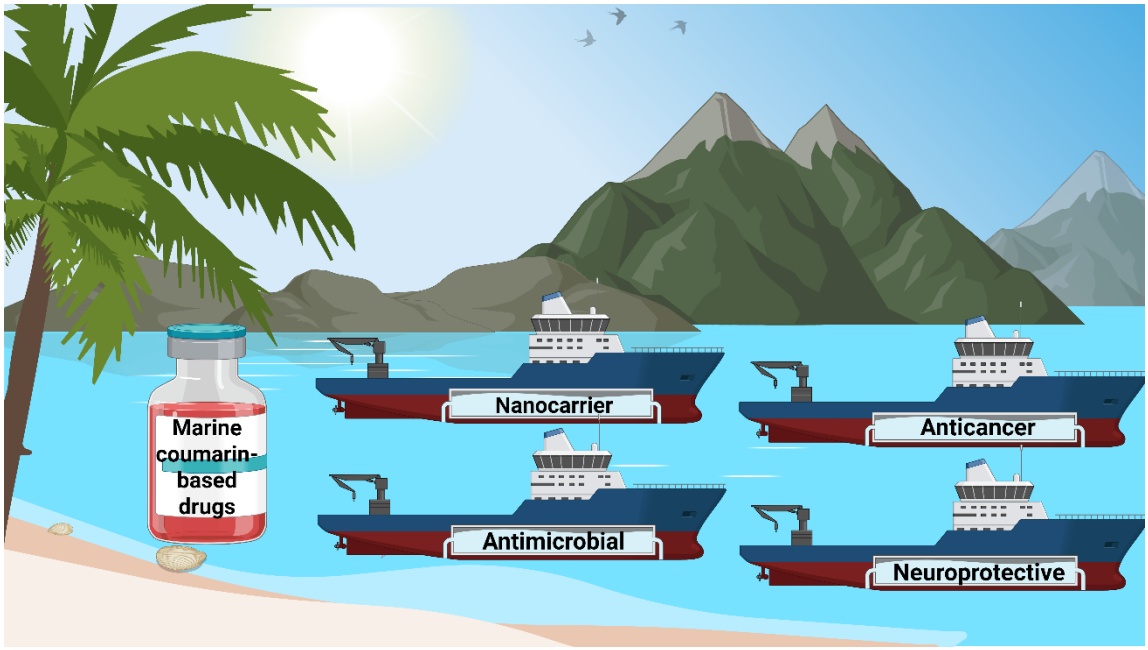


Figure 4. Drug development applications of marine-derived coumarins.

6.2. Clinical trials

Despite the large body of biomedical research conducted on traditional coumarin-based medicines, only a limited number of compounds have advanced to formal clinical evaluation. This highlights a significant gap between promising preclinical findings and successful clinical translation. In many cases, both marine-derived coumarins and structurally related analogues have been considered in clinical studies to overcome limitations related to natural abundance, stability, and pharmacokinetics[179]. Esculetin is currently in phase IV clinical trials, where its ability to modulate the atherosclerosis index is being studied as a predictive biomarker for cardiovascular disorders[180]. In parallel, daphnetin has entered phase II clinical trials to determine its efficacy and safety in managing gingivitis and oral inflammation[181]. It is also being tested in phase II studies for its role in treating secondary progressive multiple sclerosis[182]. More recently, the U.S. National Institutes of Health approved another phase II clinical trial assessing the safety and tolerability of intravenous daphnetin, administered alongside standard therapies, for adult patients suffering from severe traumatic brain injury[183]. The clinical evaluations of these coumarin-based compounds are listed in **Table 4**.

In addition to these trials, alternative pharmaceutical strategies are emerging to optimize the therapeutic use of marine coumarins. Owing to their strong antiproliferative effects, several coumarin derivatives have been encapsulated in nanocarrier systems to enhance selectivity and minimize off-target toxicity. For example, daphnetin has been successfully loaded into CD-PEI-FA/FA-NHS multifunctional liposomes, which demonstrated synergistic activity when applied in combined chemo- and photothermal cancer therapy[184]. Although natural products have historically provided many clinically approved drugs, very few marine-derived coumarins have progressed to advanced clinical stages. This gap underscores the need for intensified research efforts to expand the therapeutic portfolio of these compounds and translate their promising biological activities into approved medicines. The chemical structures of the above mentioned coumarins are illustrated in **Figure 5**.

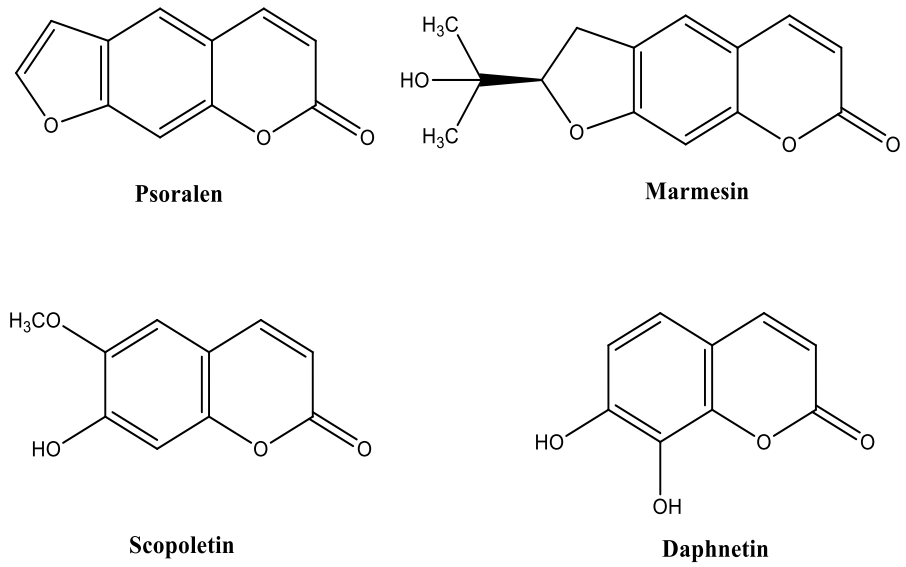


Figure 5. Chemical structures of selected coumarin derivatives investigated in oncology and clinical research, emphasizing structural elements associated with cytotoxicity, DNA interaction, and modulation of cancer-related signaling pathways.

Table 4. Clinical evaluation of coumarin-based compounds.

Compound name	Source	Indication	Clinical phase	Current status
Esculetin	Plant-derived / coumarin analogue	Cardiovascular disorders (atherosclerosis biomarker)	Phase IV	Ongoing evaluation
Daphnetin	Plant-derived / coumarin analogue	Gingivitis, oral inflammation	Phase II	Ongoing
Daphnetin (IV formulation)	Coumarin analogue	Traumatic brain injury	Phase II	Ongoing
Daphnetin	Coumarin analogue	Secondary progressive multiple sclerosis	Phase II	Ongoing
Fraxetin	Natural coumarin (reported candidate)	Benign prostatic hyperplasia	Phase III	Under clinical investigation

7. Green chemistry applications

Beyond the boundaries of medicine, marine-derived coumarins are drawing increasing attention for their versatile applications in sustainable and advanced technologies[185], as illustrated in **Figure 6**. Their intrinsic chemical properties make them valuable in green chemistry, particularly in the development of eco-friendly biomaterials and innovative dyes for sensing applications. A remarkable advancement in this regard is the integration of nanotechnology, where coumarins and structurally related analogues are being harnessed to design highly sensitive sensors and biosensors with utility across environmental, industrial, and biomedical domains[186]. The growing shift toward natural dyes further highlights the relevance of coumarins, as these molecules combine biocompatibility and biodegradability with functional efficiency[187]. Their well-documented pharmacological potential suggests that employing coumarins as structural building blocks not only promotes sustainability but also expands the scope of their application beyond therapeutics[188].

In this broader context, mondo-coumarins stand out as marine-derived meroterpenes of exceptional significance. While they are widely recognized for their diverse biological activities—including antimicrobial, antitumor, antioxidant, neuroprotective, and anti-inflammatory effects—they also hold untapped promise in materials science and nanotechnology[30]. By bridging bioactivity with material innovation, coumarins exemplify how natural compounds can drive forward both health sciences and sustainable technological progress. However, the transition of marine-derived coumarins from laboratory-scale research to industrial application is hindered by significant challenges related to scalability, cost-effectiveness, and long-term stability. The "supply problem" remains a primary bottleneck, as the concentrations of bioactive coumarins in marine biomass are often extremely low, making large-scale wild harvesting economically unviable and ecologically destructive. While chemical synthesis and microbial fermentation offer alternatives, the high costs associated with specialized precursors and low yields in bioreactors currently limit their commercial competitiveness[189]. Furthermore, the material stability of these compounds presents a technical hurdle; many marine coumarins are susceptible to photo-degradation and hydrolytic instability when integrated into industrial polymers or sensors. To overcome these barriers, future research must focus on optimizing synthetic biology platforms for high-yield production and developing protective nanocoatings that preserve the functional integrity of coumarin-based materials under diverse environmental conditions[9,34].

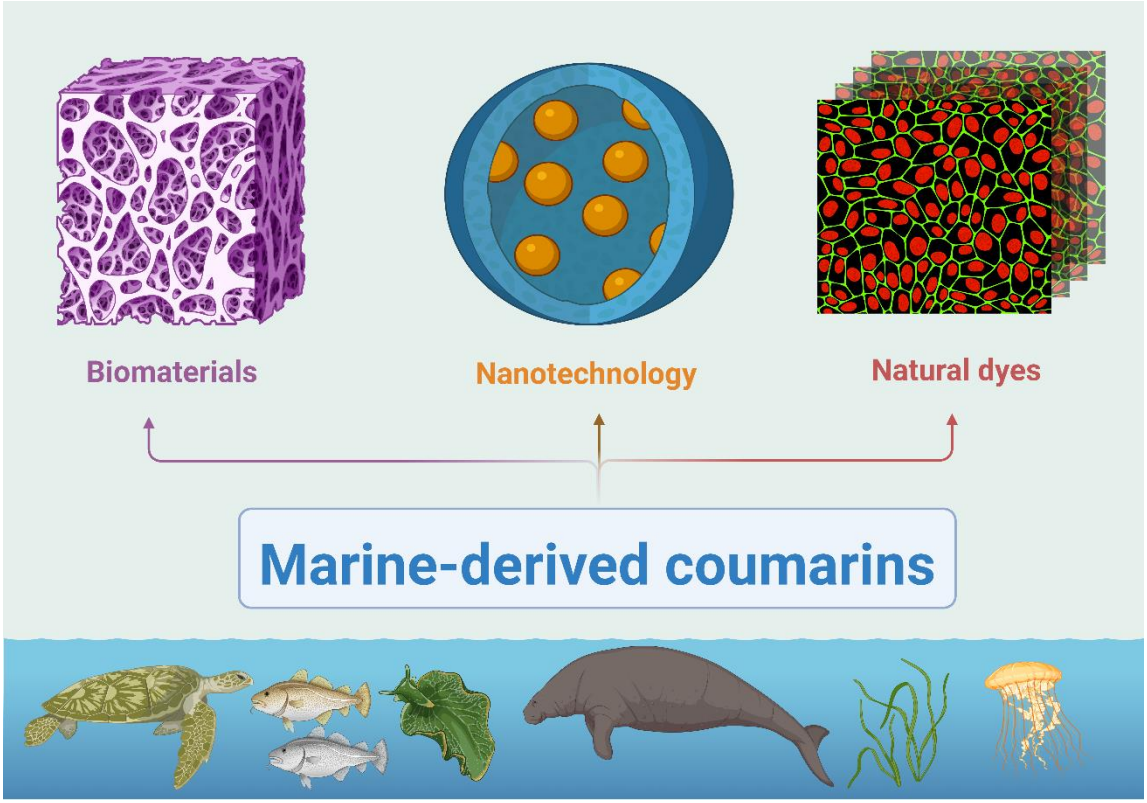


Figure 6. Applications of marine-derived coumarins in green chemistry, illustrating their roles as biodegradable materials, photoactive compounds, and functional components in catalysis, sensing systems, and environmentally friendly technologies.

7.1. Biodegradable materials

Despite their relatively simple chemical framework, coumarin-based products have become deeply embedded in daily life, with wide-ranging biomedical, biological, and environmental applications. Their prominence in medicine stems largely from their bioactivity, including potent antioxidant, anticancer, and antimicrobial effects[190]. From an environmental perspective, coumarins align closely with the principles of green chemistry due to their natural origin, environmental compatibility, and biodegradability. These attributes make them attractive scaffolds for designing novel materials that may provide innovative solutions to global environmental challenges[191]. Recent research has highlighted the potential of coumarin derivatives in the development of photoresponsive, biodegradable materials. For example, photoactive lead telluride nanocrystals coated with thiolated polyethylene glycol ligands bearing coumarin moieties have been synthesized. These nanocrystals were evaluated in photodegradation experiments against organic dyes such as methylene blue and methyl orange, demonstrating their potential utility in pollutant remediation[192].

7.2. Biotechnology-related role

Marine-derived coumarins have emerged as valuable bioactive molecules in modern biotechnology, where they serve as versatile tools for both applied and fundamental research. Their structural diversity, often enriched by halogenation and fusion with terpenoid or alkaloid moieties, provides unique chemical frameworks that can be tailored for specific applications[193]. In biocatalysis, coumarins isolated from marine fungi, algae, and invertebrates have shown promise as substrates or modulators of enzymatic processes, enabling the development of greener and more efficient catalytic systems[194]. These features make them attractive for advancing sustainable biotechnology, particularly in processes where natural product scaffolds are preferred over synthetic analogs due to their environmental compatibility[195].

In the field of bioengineering, marine-derived coumarins have been investigated as building blocks for the design of novel biomaterials. Their photoreactive and fluorescent properties enable applications in bioimaging, biosensors, and controlled drug delivery systems[196]. For example, coumarin-based linkers have

been incorporated into smart polymeric materials, where light can trigger the release of therapeutic agents in a spatially and temporally controlled manner. Such innovations highlight how the structural characteristics of marine coumarins can be harnessed to bridge chemistry with advanced biomedical technologies[197]. Moreover, the biotechnological significance of these compounds extends to environmental applications. Marine-derived coumarins incorporated into nanomaterials and biodegradable polymers have been studied for their role in pollution management, particularly in the photodegradation of organic contaminants. Their ability to couple bioactivity with photochemical responsiveness represents a unique advantage in designing multifunctional materials[198]. Collectively, these advances demonstrate that these derivatives are more than pharmacological leads—they are versatile molecular tools with a growing impact on biotechnology.

7.3. Natural dyes

Marine-derived coumarins have recently attracted interest not only for their pharmacological properties but also as promising candidates for natural dye applications. Their molecular framework, often enriched with hydroxyl, methoxy, and halogen substituents, provides a broad spectrum of colors ranging from pale yellow to deep orange and reddish-brown[199]. These chromophoric features arise from the conjugated π-electron system of the coumarin nucleus, which can undergo structural modifications that enhance light absorption and emission. Such characteristics make marine coumarins ideal for developing eco-friendly alternatives to synthetic dyes, particularly at a time when the environmental burden of petroleum-derived colorants is raising significant concerns[200].

The natural origin of marine coumarins provides an added advantage: they are typically biodegradable and exhibit low toxicity, reducing ecological impact when compared with conventional dyes. This aligns them with the principles of green chemistry and sustainable development[201]. Additionally, their photostability and capacity to bind with natural fibers, such as cotton, silk, or wool, enhance their practical utility in textile and cosmetic industries. For example, halogenated marine coumarins, produced by sponges and algae, demonstrate enhanced brightness and resistance to fading, making them attractive for long-term applications in fabric dyeing and decorative products[202]. Beyond textiles, marine-derived coumarins also show potential as natural fluorescent dyes in analytical and biomedical fields. Their ability to absorb and emit light at specific wavelengths can be harnessed for imaging, biosensing, and labeling applications[203]. In this way, they represent a sustainable dual-purpose resource—providing coloration while also contributing to advanced scientific and technological uses. Together, these attributes position marine coumarins as versatile natural dyes with applications that bridge traditional industries and modern innovations.

8. Environmental impact and sustainability

The utilization of marine-derived coumarins in green processes, material synthesis, and advanced technological applications is generally associated with the production of biodegradable byproducts that re-enter the natural environment[204]. Despite this, systematic assessments of the ecotoxicological risks posed by these benzo-α-pyrone derivatives remain limited[205]. The extent of their environmental influence is closely linked to their specific applications. For example, both naturally occurring and synthetically modified coumarins have been studied for their phytotoxic effects on sensitive plant species. When employed as herbicidal agents, coumarins can disrupt the biosynthesis of allelochemicals, thereby suppressing the formation of protective secondary metabolites. This allelopathic mechanism reduces the stress tolerance of target plants and alters their adaptive responses. Evaluating the ecological footprint and sustainability of coumarin-based applications is therefore critical[206]. Given their inherent biodegradability, the integration of coumarins into pharmaceuticals and technologies aligns with circular economy principles, simultaneously reducing potential environmental hazards[207]. Furthermore, the marine ecosystem, characterized by its dynamic chemical diversity, provides a vital source of structurally unique coumarins—particularly brominated variants—that evolve under diverse ecological pressures. This diversity highlights the ocean's

role as a reservoir of bioactive natural products, supporting innovation in biomedicine, environmentally friendly chemistry, and novel technological platforms[208].

8.1. Ecological considerations

The biosynthesis of biologically active compounds by marine organisms is essential for their adaptation and survival in complex aquatic ecosystems. These metabolites function primarily as chemical defenses, enabling species to resist predation, microbial invasion, and other ecological pressures[209]. Beyond self-protection, they also mediate interspecies and intraspecies interactions, often by being released into the surrounding environment where they influence ecological dynamics. Coumarins of marine origin are notable in this regard, as many of them exhibit well-defined ecological roles[210]. Consequently, understanding their environmental fate is critical when considering their biomedical exploitation or large-scale synthetic production. Growing concerns have emerged about the release of natural coumarins and their synthetic analogs—especially those that are poorly metabolized—into marine habitats, where they may adversely affect aquatic organisms and, indirectly, human health[211].

Despite their broad use and growing pharmaceutical interest, the environmental persistence and ecological footprint of coumarins remain insufficiently studied. A rigorous sustainability assessment requires detailed insights into their bioaccumulation, degradation, and toxicity profiles[212]. Additionally, the indiscriminate extraction of marine resources risks disturbing fragile ecosystems and accelerating biodiversity loss. This has shifted recent scientific attention toward green chemistry approaches and sustainable production strategies aimed at reducing ecological impact[213]. However, these derivatives remain non-renewable resources with inherently limited availability, making their long-term sustainable use challenging[214]. Their procurement still depends largely on harvesting local populations, a practice that can lead to ecological strain. For example, excessive collection of *Cnestis humilis* peels—rich in linear and angular furanocoumarins and pyranocoumarins—poses risks of habitat imbalance and resource depletion[215].

8.2. Sustainable harvesting practices

The growing interest in marine-derived coumarins as bioactive compounds has underscored the need for sustainable strategies to secure their supply without threatening marine ecosystems, as displayed in **Figure 7**. Unlike terrestrial plants, where cultivation can provide renewable access to secondary metabolites, many marine organisms—such as sponges, ascidians, and corals—are slow-growing and highly sensitive to ecological disturbances[216]. Direct extraction from wild populations risks habitat degradation and biodiversity loss, making sustainable harvesting a critical priority in marine natural product research. One approach to sustainability involves the development of controlled aquaculture systems for marine organisms known to produce coumarins. Mariculture techniques allow continuous cultivation under regulated conditions, reducing the pressure on natural populations while ensuring reproducible yields of desired metabolites[217]. For microbial sources, fermentation-based production offers an even more practical solution. Endophytic and symbiotic marine microbes can be isolated and cultured in laboratory conditions, where optimized growth media and bioreactor technologies support scalable biosynthesis of coumarins[218].

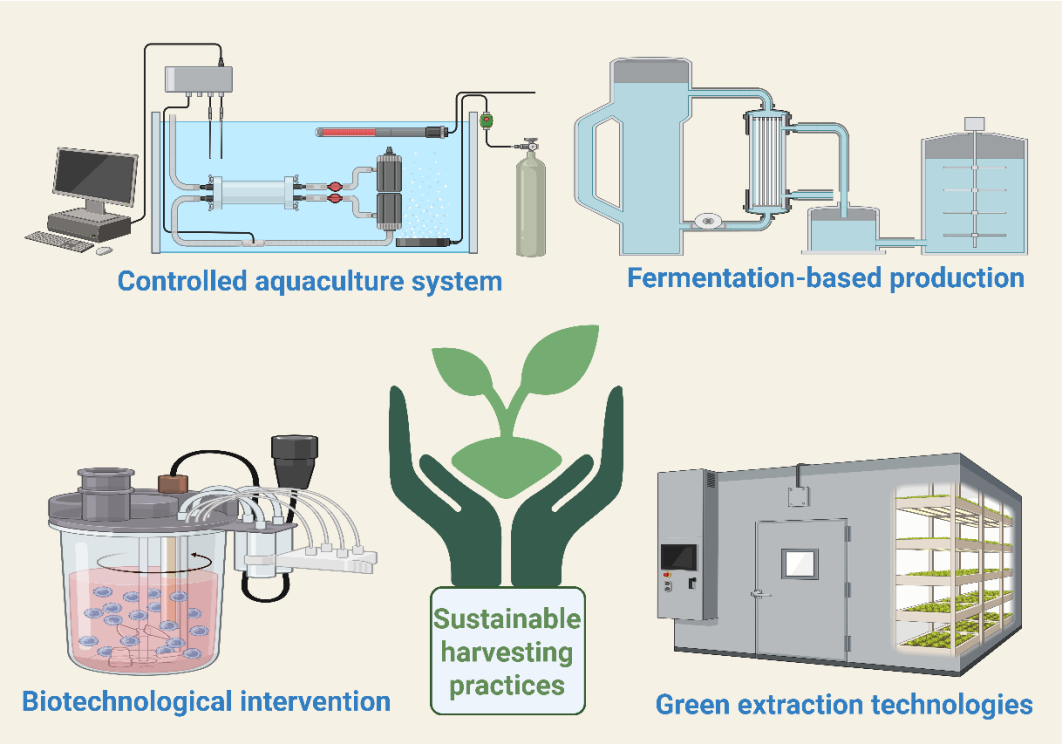


Figure 7. Integrated strategies for sustainable production of marine-derived coumarins, including marine organism cultivation (mariculture), microbial fermentation, synthetic biology approaches, and green extraction technologies.

Another promising avenue lies in biotechnological interventions, particularly the use of genetic engineering and synthetic biology[219]. Biosynthetic gene clusters responsible for coumarin production can be transferred into heterologous hosts such as *Escherichia coli* or yeast, enabling industrial-level production through fermentation[220,221]. This strategy not only bypasses ecological disruption but also allows for structural tailoring of coumarins, producing novel derivatives with improved pharmacological profiles. Additionally, green extraction technologies are being adopted to minimize environmental footprints during isolation processes. Methods such as supercritical CO_2 extraction, pressurized liquid extraction, and microwave-assisted extraction reduce the need for toxic solvents and lower energy consumption[222–224]. Combined with life-cycle assessments, these techniques ensure that the pursuit of marine coumarins aligns with the principles of environmental stewardship and circular bioeconomy. Ultimately, the sustainable harvesting of marine-derived coumarins requires an integrated framework that couples conservation policies with scientific innovation[225–227]. Collaborative efforts between marine ecologists, chemists, and policymakers are essential to balance the dual goals of drug discovery and ocean preservation. By embracing eco-conscious practices, researchers can ensure that marine-derived coumarins remain a renewable and ethically sourced resource for future biomedical and technological applications[228–230].

9. Future directions in research

Marine-derived coumarins represent a remarkable platform for innovation across biomedicine, green chemistry, and advanced technologies. Their ability to engage in hydrogen bonding and coordination interactions makes them highly adaptable ligands, suitable for integration into sensors, catalytic systems, and other functional devices. These versatile applications are largely attributed to the distinctive physicochemical properties of the coumarin scaffold, which can be harnessed not only for developing new therapeutic agents but also for advancing sustainable chemical practices and technological solutions. The growing scientific attention toward marine coumarins is strongly linked to their broad biological potential, as many of them exhibit antimicrobial, anticancer, and antioxidant activities, thereby enriching modern drug discovery pipelines.

From a synthetic perspective, rational modification of these chromophores provides a powerful route to generating novel analogues with enhanced activity spectra and improved affinity toward biomolecular targets. The incorporation of nanotechnology further expands these opportunities, enabling the design of coumarin-based materials with superior bioactivity and delivery properties. However, the natural occurrence of coumarins in diverse marine organisms raises ecological concerns, particularly when large-scale extraction is considered for pharmaceutical, catalytic, or photovoltaic purposes. To reconcile the benefits of these compounds with sustainability, alternative strategies are gaining importance. Among them, the use of tissue culture techniques to cultivate coumarin-producing organisms has emerged as a promising and eco-friendly approach, reducing the environmental burden while ensuring a reliable supply of these valuable metabolites.

10. Challenges and limitations

Despite the remarkable progress achieved in the isolation, synthesis, and functional investigation of coumarins over the past three centuries, several challenges and limitations remain unresolved. The pioneering work of Vogel, who first isolated coumarin from *Dipteryx odorata* in 1820, laid the foundation for coumarin research[231]. Yet, more recent explorations of marine-derived coumarins continue to face practical and scientific constraints. Their unique features—ranging from photophysical and photochemical reactivity to fluorescence and antibacterial potential—have positioned natural coumarins as promising scaffolds for biomedicine, sustainable chemistry, and advanced material technologies. However, the translation of both commercially available and newly isolated derivatives into real-world applications is still met with significant obstacles.

Marine-derived coumarins have demonstrated diverse biological activities, and they show considerable promise in generating fluorescent probes and therapeutic agents. Nevertheless, their practical deployment requires caution, not only due to ecological concerns but also because of socioeconomic and regulatory barriers. Clinical evaluation remains a crucial step toward therapeutic translation, yet the stringent and often prolonged regulatory frameworks surrounding natural product–based drug development continue to delay their entry into the market. Furthermore, large-scale commercial exploitation of these marine bioresources may not always align with economic feasibility in the current global economy. As a result, while the integration of marine natural coumarins into industrial and biomedical domains represents a highly attractive prospect, it continues to be an ambitious and elusive goal.

10.1. Regulatory issues

The discovery and development of new drugs is a lengthy and resource-intensive process that demands rigorous evaluation to confirm both therapeutic benefit and patient safety. Regulatory authorities, including the U.S. Food and Drug Administration and the European Medicines Agency, mandate comprehensive preclinical and clinical testing. These assessments involve a combination of *in vitro* and *in vivo* pharmacological studies designed to establish efficacy, toxicity profiles, and pharmacokinetic behavior. As a result of these stringent requirements, only a limited fraction of candidate molecules successfully progress through the development pipeline to achieve clinical approval. A further complication arises from the continual emergence of microbial resistance to existing therapies, underscoring the urgent need for innovative drugs that act through novel mechanisms.

Marine natural products represent a promising reservoir of bioactive compounds, many of which display noteworthy pharmacological potential. However, their structural complexity, large molecular size, or low natural abundance can pose significant barriers to drug development. Extracting sufficient quantities of these compounds from marine organisms is often impractical and economically unfeasible. Moreover, large-scale harvesting of macro-organisms, if not carefully managed, may impose serious ecological risks and contribute to environmental degradation. To overcome these limitations, alternative approaches such as total chemical

synthesis, microbial fermentation, or sustainable aquaculture are increasingly being explored as viable strategies to secure reliable and eco-friendly supplies of marine-derived drug candidates.

10.2. Market barriers

Marine-derived coumarins, despite their broad biological and technological potential, face several barriers that limit their entry into commercial markets. One of the foremost challenges is supply and scalability. Most coumarins isolated from marine organisms occur in trace amounts, making large-scale extraction both costly and inefficient. Cultivating marine organisms such as fungi, corals, or ascidians under controlled laboratory or industrial conditions often requires specialized infrastructure and long growth cycles, further complicating consistent production. Although synthetic and semi-synthetic approaches provide alternatives, these methods may not fully replicate the structural diversity of natural marine metabolites, creating a gap between laboratory discoveries and market feasibility[232].

Economic and technical barriers also play a decisive role. The high costs of isolation, purification, and characterization—often requiring advanced chromatographic and spectroscopic methods—limit industrial uptake, especially in low- to middle-income markets. Furthermore, the chemical instability of certain coumarins under light or oxidative conditions complicates formulation and storage, reducing their appeal compared with more stable synthetic alternatives. Intellectual property issues further restrict commercialization, as the uniqueness of structures derived from marine organisms can lead to disputes regarding patents and benefit-sharing under international agreements such as the Nagoya Protocol. Finally, market awareness and industry readiness are still limited. While academic literature increasingly highlights the pharmacological and technological value of marine-derived coumarins, many industries remain hesitant to adopt them due to a lack of standardized supply chains, unclear return on investment, and limited consumer demand for marine-sourced bioactives compared to plant-derived compounds. Without strong partnerships between academia, biotech firms, and industrial stakeholders, the commercialization of marine coumarins risks remaining confined to niche applications rather than achieving widespread impact.

11. Case studies of successful applications

The incorporation of natural coumarins and psoralens into commercial products, particularly cosmetics, has created significant opportunities for their functional modification and for the development of novel derivatives. A notable example comes from Boiron, which has advanced fraxetin, into Phase III clinical trials. This compound is being evaluated against α-blockers for the treatment of moderate urinary symptoms associated with benign prostatic hyperplasia, underscoring the clinical potential of coumarin-based molecules. Moreover, the ubiquity of the coumarin chromophore in approved drugs and its emerging applications in nanotechnology highlight the strategic advantage of integrating coumarin scaffolds at the early stages of synthetic drug design. Beyond biomedicine, coumarins also contribute meaningfully to environmental sustainability and advanced technologies. Their strong fluorescent properties support applications in sensing and imaging, while their role in biosourced polymers offers solutions to global challenges such as reducing carbon dioxide emissions. Coumarin-derived monomers have been employed in the synthesis of biodegradable plastics and in the design of polymeric frameworks capable of capturing and sequestering carbon dioxide. In addition, the photosensitivity of coumarins and psoralens has been harnessed to produce smart coatings with responsive optical and protective properties, further expanding their technological relevance.

12. Conclusion

Marine-derived coumarins represent a structurally diverse and pharmacologically interesting class of natural products with potential applications in biomedicine, green chemistry, and advanced material science. The unique ecological conditions of marine environments contribute to structural variations such as

halogenation, prenylation, and extended conjugation, which may influence the biological and physicochemical properties of these compounds. Experimental studies have demonstrated a broad spectrum of activities, including antimicrobial, anticancer, antioxidant, anti-inflammatory, and neuroprotective effects, while their fluorescence and photoactive properties support emerging applications in sensing technologies, nanomedicine, and sustainable materials. Despite these promising findings, several important limitations remain. Most currently available evidence is derived from *in vitro* investigations, whereas *in vivo* validation and clinical translation remain limited. Variability in extraction methods, compound characterization, experimental models, and origin classification also complicates direct comparison between studies. In addition, issues related to sustainable sourcing, low natural abundance, scalability of production, pharmacokinetics, selectivity, and potential toxicity continue to represent major translational challenges. Although some coumarin-based compounds and analogues have advanced into clinical evaluation, marine-derived coumarins themselves remain largely at the preclinical stage. Future progress in this field could require standardized biological evaluation, deeper mechanistic studies, sustainable production strategies, and integration of synthetic biology, nanotechnology, and medicinal chemistry approaches. Overall, marine-derived coumarins should be regarded as promising yet still developing candidates whose ultimate biomedical and technological value will depend on successful resolution of these scientific and translational barriers.

Conflict of interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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