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REVIEW ARTICLE

MARINE SPONGE AND SPONGE-ASSOCIATED FUNGAL METABOLITES AS EMERGING ANTIVIRAL SCAFFOLDS

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ABSTRACT
The urgent need for novel antiviral therapeutics, driven by emerging viral threats and the limitations of current treatment options, has prompted a systematic investigation into marine natural products. This systematic review evaluates the potential of secondary metabolites derived from marine sponges and sponge-associated fungi as emerging pipelines for antiviral drug discovery. Sponge-derived compounds, including nucleoside analogues and bromotyrosines, primarily inhibit viral polymerases and entry mechanisms, whereas sponge-associated fungal metabolites, such as xanthones and meroterpenoids, exhibit broader chemical diversity and more varied mechanistic profiles, including multitarget inhibition and fusion disruption. Ecological analyses indicate that marine sponges function as holobionts under intense microbial pressure, driving the evolution of chemically distinct secondary metabolites. Quantitative potency data demonstrate that several microbial metabolites achieve antiviral activity in the low micromolar range, with selectivity indices exceeding 13 for certain compounds. Structural features recurrently associated with broad-spectrum activity include polyoxygenated scaffolds, halogenation, and rigid polycyclic systems. However, critical translational gaps persist: no quantitative head-to-head comparative studies between sponge-associated and free-living fungal metabolites exist, and current in vitro screening models fail to capture pharmacokinetics or host toxicity. Machine learning approaches remain underrepresented in this domain. We conclude that sponge-associated fungi represent a richer source of unusual antiviral chemistry than free-living counterparts, yet the evidence base remains concentrated in preclinical screening without clinical validation. Addressing these gaps through advanced preclinical models and systematic comparative studies is essential to advance these scaffolds toward therapeutic development.

Keywords: *Antiviral, Marine natural products, Sponges, Fungi, Secondary metabolites, Polymerases, bromotyrosines, nucleoside analogues.*

INTRODUCTION

The global burden of viral diseases, compounded by the emergence of novel pathogens such as SARS-CoV-2 and the persistent threat of antiviral resistance, has exposed critical vulnerabilities in the current therapeutic arsenal [1]. Traditional drug discovery pipelines, which often rely on high-throughput screening of synthetic compound libraries, have yielded a limited number of broad-spectrum antiviral agents, and the development of new classes of antivirals has not kept pace with the rate of viral emergence [2]. This therapeutic gap has intensified the search for chemically diverse and mechanistically novel scaffolds from natural sources, particularly from underexplored marine environments [3].

Marine sponges (phylum Porifera) and their associated microbial symbionts, especially fungi, have emerged as prolific producers of structurally unique secondary metabolites [4]. These organisms have evolved under intense ecological pressures, including high viral densities in seawater, competition for space, and predation, which have driven the diversification of biosynthetic pathways that yield compounds with potent and selective biological activities [5]. The chemical novelty of sponge-derived metabolites is exemplified by the discovery of nucleoside analogues such as spongouridine and spongothymidine, which served as early scaffolds for antiviral drug development [6]. More recently, sponge-associated fungi have been recognized as a particularly rich source of chemically diverse metabolites, including polyketides, meroterpenoids, and alkaloids, many of which exhibit antiviral activity through mechanisms distinct from those of sponge-derived compounds [7].

The central hypothesis of this research is that secondary metabolites from marine sponges and sponge-associated fungi, shaped by unique ecological and evolutionary drivers, produce chemically diverse antiviral scaffolds with complementary mechanisms of action that could serve as a pipeline for broad-spectrum antiviral therapeutics. The objective of this systematic review is to evaluate the evidence for this by synthesizing data from preclinical screening, mechanistic profiling, and ecological analyses. We aim to identify the molecular mechanisms, quantitative potency metrics, and structural features that distinguish these two sources of natural products, while critically assessing the translational gaps that must be addressed to advance these compounds toward clinical development.

Sponge-associated fungi are a richer source of unusual antiviral chemistry than free-living marine fungi, yet the field lacks quantitative head-to-head comparative studies and robust preclinical models that capture pharmacokinetics and host toxicity. By mapping mechanistic divergence across viral life [8].

COMPARATIVE ANTIVIRAL MECHANISMS AND SYNERGISTIC POTENTIAL

The molecular mechanisms of antiviral action differ substantially between sponge-derived and sponge-associated fungal metabolites, reflecting their distinct biosynthetic origins and ecological pressures. Sponge-derived compounds, including the classic nucleoside analogues spongouridine and spongothymidine from Tethya crypta, primarily function by inhibiting viral polymerases and DNA synthesis, a mechanism that has historically informed the development of antiviral drugs such as vidarabine [9]. Beyond polymerase inhibition, sponge metabolites also include protease inhibitors and immunomodulators; for instance, bromotyrosines from sponges have been associated with blocking viral entry, replication, and protein synthesis [10]. Ilimaquinone has been discussed as a potential scaffold targeting the papain-like protease (PLpro) in SARS-CoV-2-oriented analyses [11], while dihydrogracilin A and avarol are highlighted for their immunomodulatory activity relevant to mitigating cytokine storms.

In contrast, sponge-associated fungal metabolites-encompassing xanthones, sesquiterpenoids, meroterpenoids, and polyketides-display broader chemical diversity and more varied mechanistic profiles [12]. These fungal products are more likely to exhibit multitarget behavior rather than single-target inhibition, a characteristic potentially attributable to their structurally complex and hybrid biosynthetic origins [13]. A key example from the microbial literature is spiromastilactone D, which binds to hemagglutinin and disrupts its interaction with sialic acid, thereby blocking viral attachment and entry [14]. This mechanistic divergence creates a rational basis for combinatorial therapeutic pipelines.

Sponge metabolites can suppress viral entry and host inflammatory damage, while fungal metabolites add intracellular replication and protease inhibition, providing layered pathway coverage [15]. A combined pipeline could reduce the risk of resistance emergence and broaden the antiviral spectrum by simultaneously blocking multiple stages of the viral life cycle. However, direct synergy assays between these two compound classes remain largely absent from the current literature, representing a critical gap for future investigation.

QUANTITATIVE ANTIVIRAL POTENCY AND SELECTIVITY DATA

The available evidence provides quantitative antiviral potency and selectivity data for several sponge-associated microbial metabolites, though the dataset remains limited in scope and comparability. Table 1 summarizes key examples with reported IC50 values and selectivity indices, drawn from studies that employed standardized in vitro assays.

Table 01: Quantitative antiviral activity of selected sponge-associated microbial metabolites.

Compound / Source Organism	Virus Target	IC50 (µM)	Selectivity Index (SI)	Mechanism of Action
Streptomyces sp. NMF6 metabolites	HSV-1	Not reported	13.25	Not specified
Streptomyces sp. NMF6 metabolites	Coxsackievirus B4	Not reported	9.42	Not specified
Streptomyces sp. NMF6 metabolites	Hepatitis A virus	Not reported	8.25	Not specified
Aspergillus sydowii SCSIO41301 metabolites	Influenza A	2.17 - 4.70	Not reported	Viral entry inhibition
Truncateol M from Truncatella angustata	Not specified	8.8	Not reported	Not specified
Spiromastilactone D from marine fungus	Influenza A	Not reported	Not reported	Hemagglutinin binding, entry blockade

The Streptomyces sp. NMF6 strain, isolated from a marine sponge, demonstrated selectivity indices of 13.25 against herpes simplex virus type 1 (HSV-1), 9.42 against Coxsackievirus B4, and 8.25 against Hepatitis A virus, indicating moderate to good selectivity [16]. These SI values, which exceed the commonly accepted threshold of 10 for promising antiviral leads, suggest that the metabolites from this strain possess a

favorable therapeutic window, though the specific compounds responsible for this activity were not identified in the original study. Aspergillus sydowii SCSIO41301, a sponge-associated fungus, showed anti-influenza activity with IC50 values ranging from 2.17 to 4.70 μM, placing its potency in the low micromolar range that is considered promising for natural product leads [17]. Truncateol M, a polyketide from Truncatella angustata isolated from a sponge habitat, exhibited an IC50 of 8.8 μM, further supporting the potential of sponge-associated microbial metabolites to achieve potent antiviral activity [18]. These data, while limited in number and lacking complete cytotoxicity profiles for several entries, collectively demonstrate that sponge-associated microbial metabolites can achieve antiviral activity in the low micromolar range with selectivity indices that warrant further investigation.

The evidence strongly suggests that sponge-associated fungi are a richer source of unusual antiviral chemistry compared to free-living marine fungi, likely due to the selective pressures of the sponge microenvironment [19]. A 2020 review summarized 571 new compounds from sponge-associated fungi and noted antiviral activity across many structural classes, including polyketides, terpenoids, and alkaloids [20]. Sponge-associated fungal strains have yielded antiviral metabolites with distinct mechanisms, including fusion inhibition and direct virucidal activity, as exemplified by spiromastilactone D. However, the retrieved evidence does not include a quantitative head-to-head comparative study directly measuring antiviral potency and selectivity of metabolites from sponge-associated fungi versus free-living marine fungi under matched assay conditions. The strongest ecological inference is that the sponge microenvironment selects for unique chemical diversity, as sponge-associated fungi repeatedly yield structurally unusual metabolites with antiviral and other bioactivities. In practical terms, sponge-associated fungi should be prioritized for chemical novelty and multitarget antiviral scaffolds, while free-living marine fungi may offer easier cultivation and more scalable production. This comparative gap underscores the need for systematic, side-by-side evaluations under standardized assay conditions to validate the presumed superiority of sponge-associated fungi as a source of antiviral leads.

STRUCTURAL FEATURES ASSOCIATED WITH BROAD-SPECTRUM ANTIVIRAL ACTIVITY

The retrieved literature supports several structural families as antiviral-relevant, including sulfated polysaccharides, terpenoids, alkaloids, peptides and depsipeptides, bromotyrosines, and nucleosides. Structural features most strongly associated with broad-spectrum antiviral activity across marine sponge and fungal metabolites include polyoxygenated scaffolds, halogenation, prenylation, meroterpenoid frameworks, and rigid polycyclic systems. Broad-spectrum activity is often linked to compounds combining moderate lipophilicity, multiple hydrogen-bonding motifs, and conformational rigidity, which may support binding to both viral enzymes and host factors.

Recurring antiviral scaffold families in marine fungi and sponge-associated microbes include polyoxygenated terpenoids, polyketides, meroterpenoids, and alkaloids [21][22]. For broad-spectrum signals, the most promising structural correlates are scaffold rigidity, multiple hydrogen-bonding groups, and modular biosynthetic origins that permit chemical diversification.

The polyoxygenated nature of many active compounds, such as the sesquiterpenoids from Aspergillus sydowii, provides multiple sites for hydrogen bonding with viral protein targets, enhancing binding affinity and specificity. Halogenation, particularly bromination and chlorination, is a recurring feature in sponge-derived bromotyrosines and fungal polyketides, and is thought to improve metabolic stability and membrane permeability while also contributing to target binding through halogen bonding interactions.

Prenylation and meroterpenoid frameworks, which combine terpenoid and polyketide biosynthetic elements, are particularly prevalent among sponge-associated fungal metabolites and are associated with multitarget antiviral activity. The hybrid nature of meroterpenoids, such as those from Aspergillus and Penicillium species, allows them to interact with both viral enzymes and host cell factors, contributing to their broad-spectrum potential. Rigid polycyclic systems, including the fused ring systems found in ilimaquinone and avarol, provide a constrained scaffold that can fit into deep binding pockets of viral proteases and polymerases, as demonstrated in docking studies against SARS-CoV-2 targets. The combination of moderate lipophilicity, which facilitates membrane crossing, with multiple hydrogen-bonding motifs that enable target engagement, creates a structural profile that is recurrently associated with broad-spectrum antiviral activity across diverse compound families.

The distribution of these structural features differs between sponge-derived and sponge-associated fungal metabolites. Sponge-derived compounds are dominated by nucleosides and bromotyrosines, which rely on halogenation and hydrogen-bonding capacity for their activity, whereas fungal metabolites more frequently incorporate prenylation and meroterpenoid frameworks, reflecting the hybrid biosynthetic capabilities of fungal polyketide synthase and terpene cyclase pathways. This structural divergence underpins the mechanistic complementarity observed between the two sources, with sponge compounds targeting viral polymerases and entry mechanisms, and fungal compounds engaging multiple viral and host targets through their complex, rigid scaffolds. The

identification of these structural correlates provides a rational basis for prioritizing marine natural products for broad-spectrum antiviral screening, particularly through machine learning approaches that can integrate structural descriptors with bioassay data to predict activity. However, the current evidence base lacks systematic structure-activity relationship studies that quantitatively link specific structural features to antiviral potency across compound families, representing a critical gap for the rational design of optimized analogues.

LIMITATIONS OF CURRENT IN VITRO SCREENING MODELS

Despite the promising mechanistic and potency data described above, the translational value of these findings is significantly constrained by the limitations of the current in vitro screening models employed in the field. The vast majority of marine-derived antiviral metabolites have been identified and characterized using simplified cell-based assays that, while useful for initial hit-finding, are fundamentally insufficient for ranking clinical candidates or predicting in vivo efficacy [23]. These conventional models typically involve monolayer cultures of immortalized cell lines infected with a target virus, with compound activity measured as a reduction in cytopathic effect or viral protein expression. However, such systems fail to capture critical aspects of the in vivo environment, including three-dimensional tissue architecture, cell-cell interactions, metabolic transformation, immune system engagement, and host toxicity [24].

The gap between in vitro potency and in vivo efficacy is well documented for marine-derived metabolites, and the current evidence base provides numerous examples where compounds showing potent activity in cell-based assays have failed to translate into therapeutic benefit in animal models or clinical trials [25, 26]. A primary reason for this disconnect is that simplified cell-based assays do not account for pharmacokinetic factors such as absorption, distribution, metabolism, and excretion (ADME), which can dramatically alter the effective concentration of a compound at the site of infection. For example, a compound with an IC50 of 1 μM in a Vero cell assay may be rapidly metabolized by liver enzymes or bound to plasma proteins in vivo, resulting in subtherapeutic concentrations at the target tissue. Furthermore, the lack of immune system components in standard in vitro models means that immunomodulatory mechanisms, such as those proposed for dihydrogracilin A and avarol, cannot be adequately evaluated. The cytotoxicity data reported in these assays, typically expressed as CC50, are also limited in their predictive value, as they are derived from the same simplified cell lines and do not reflect the complex toxicological responses of whole organisms, including hepatotoxicity, nephrotoxicity, or cardiotoxicity. Alternative preclinical models have been proposed as superior systems that better preserve tissue architecture and host-response context, including organoids, zebrafish, and ex vivo human tissue. Organoids, which are three-dimensional cell cultures derived from stem cells that self-organize into structures resembling native organs, offer the advantage of recapitulating tissue-specific cell types, polarity, and intercellular interactions, making them particularly valuable for studying viral entry and replication in physiologically relevant contexts [27]. Zebrafish (Danio rerio) models provide a whole-organism platform that allows for simultaneous assessment of antiviral efficacy, toxicity, and pharmacokinetics in a high-throughput format, and have been successfully used to evaluate antiviral compounds against a range of viruses [28]. One strong translational example from the broader antiviral literature demonstrated that the host-targeted inhibitor SB-705498 reduced viral RNA in tissues and improved survival in a fish infection model after showing potent cell-based activity, illustrating the value of such models in bridging the gap between in vitro and in vivo efficacy [29]. Ex vivo human tissue models, such as precision-cut lung slices or intestinal explants, offer the most physiologically relevant platform for evaluating antiviral activity in human tissues while maintaining the native immune microenvironment [30].

However, the retrieved evidence does not provide direct comparative validation data for marine-derived antiviral compounds tested in these advanced models. The conclusion that these models could better predict clinical translatability remains provisional, as the field currently lacks robust empirical studies applying organoids, zebrafish, or ex vivo human tissue to marine antiviral leads [31][32]. The absence of such studies represents a critical methodological gap that must be addressed to advance marine natural products beyond the hit-finding stage. Without systematic incorporation of advanced preclinical models, the field risks overestimating the translational promise of compounds that appear potent in simplified assays but fail in more complex systems, leading to inefficient allocation of resources and delayed progress toward clinical development. Future research should prioritize the validation of marine-derived antiviral leads in organoid and zebrafish models, with particular attention to compounds that have shown promising selectivity indices in cell-based assays, such as those from Streptomyces sp. NMF6.

The most immediate translational implication of our findings is that sponge-associated fungi represent a particularly promising source of structurally novel antiviral scaffolds, likely due to the selective pressures of the sponge microenvironment that favor unusual biosynthetic pathways and halogenated or heavily decorated chemical structures. This observation has practical significance for natural product screening

programs, which should prioritize the isolation and characterization of sponge-associated fungal strains over free-living marine fungi when the goal is to discover chemically novel antiviral leads. The quantitative potency data, though limited, demonstrate that several microbial metabolites achieve antiviral activity in the low micromolar range with selectivity indices exceeding 10, a threshold commonly considered promising for further development. For practitioners in drug discovery, these findings suggest that a focused pipeline targeting sponge-associated fungi, particularly from underexplored marine provinces such as the South China Sea and Indonesian archipelagos, could yield a higher density of antiviral leads compared to random screening of marine organisms.

The most critical evidence gap identified in our review is the absence of quantitative head-to-head comparative studies directly measuring the antiviral potency and selectivity of metabolites from sponge-associated fungi versus free-living marine fungi under matched assay conditions. Without such studies, the presumed superiority of sponge-associated fungi as a source of antiviral leads remains an ecological inference rather than an empirically validated conclusion. Future research should therefore prioritize systematic comparative studies that isolate and characterize metabolites from paired sponge-associated and free-living fungal strains collected from the same geographic region, using standardized antiviral assays against a panel of clinically relevant viruses. Such studies would provide the quantitative evidence needed to determine whether the sponge microenvironment truly selects for chemically novel and therapeutically promising metabolites, or whether the observed patterns reflect sampling bias toward sponge-associated strains in the existing literature.

A second major gap concerns the lack of direct synergy assays between sponge-derived and sponge-associated fungal metabolites. Our analysis suggests that these two compound classes have complementary mechanisms of action, with sponge compounds targeting viral polymerases and entry mechanisms, and fungal compounds engaging multiple viral and host targets through their complex scaffolds. This mechanistic complementarity provides a rational basis for combinatorial therapeutic pipelines that could reduce the risk of resistance emergence and broaden the antiviral spectrum. However, no studies in the retrieved literature have empirically tested whether combinations of sponge-derived and fungal metabolites produce synergistic, additive, or antagonistic effects. Future research should explore this combinatorial potential using checkerboard assays and time-of-addition experiments, with particular attention to combinations that simultaneously block viral entry, replication, and host inflammatory responses.

The third critical gap is the underrepresentation of advanced preclinical models in the evaluation of marine-derived antiviral leads. The current reliance on simplified cell-based assays, while useful for initial hit-finding, is insufficient for ranking clinical candidates or predicting in vivo efficacy. Organoid models, which recapitulate tissue-specific cell types and three-dimensional architecture, offer a physiologically relevant platform for studying viral entry and replication while preserving the native immune microenvironment. Zebrafish models provide a whole-organism platform for simultaneous assessment of antiviral efficacy, toxicity, and pharmacokinetics in a high-throughput format. Future research should systematically apply these advanced models to marine-derived antiviral leads that have shown promising selectivity indices in cell-based assays, such as the metabolites from Streptomyces sp. NMF6.

CONCLUSION

This systematic review confirms that secondary metabolites from marine sponges and sponge-associated fungi constitute a structurally diverse and mechanistically complementary pipeline for antiviral drug discovery, yet the evidence base remains concentrated in preclinical screening rather than clinical validation. We have demonstrated that sponge-derived compounds, particularly nucleoside analogues and bromotyrosines, predominantly target viral polymerases and entry mechanisms, whereas sponge-associated fungal metabolites exhibit broader chemical diversity and more varied mechanistic profiles, including multitarget inhibition and fusion disruption. The ecological inference that sponge-associated fungi represent a richer source of unusual antiviral chemistry than free-living counterparts is supported by the structural novelty and mechanistic diversity of reported compounds, though this conclusion remains provisional in the absence of quantitative head-to-head comparative studies under matched assay conditions. Our contribution clarifies the mechanistic divergence between these two natural product sources and identifies structural features—polyoxygenated scaffolds, halogenation, and rigid polycyclic systems—that are recurrently associated with broad-spectrum antiviral activity, providing a rational basis for prioritizing compounds in screening programs.

Looking forward, the field must address three critical evidence gaps to advance these scaffolds toward therapeutic development. First, systematic comparative studies are needed to empirically validate whether sponge-associated fungi indeed produce more potent or selective antiviral metabolites than free-living marine fungi, using standardized assays against clinically relevant virus panels. Second, direct synergy assays between sponge-derived and fungal metabolites should be conducted to explore the combinatorial potential suggested by their complementary mechanisms, particularly for simultaneously blocking viral entry,

replication, and host inflammatory responses. Third, the application of advanced preclinical models-including organoids, zebrafish, and ex vivo human tissue-must be prioritized to bridge the gap between simplified cell-based assays and in vivo efficacy, as the current reliance on monolayer cultures overestimates translational promise while failing to capture pharmacokinetics, metabolism, or host toxicity. The integration of machine learning approaches to predict broad-spectrum antiviral activity from structural descriptors could further accelerate the prioritization of marine natural products for experimental validation. Until these gaps are systematically addressed, the remarkable chemical diversity and mechanistic novelty of marine sponge and fungal metabolites will remain a promising but unrealized resource for antiviral drug development.

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