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Antimicrobial metabolites from marine sponge-associated actinobacteria: Evidence, translational gaps, and prospects for food biopreservation

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Abstract
Marine sponge-associated Actinobacteria are important sources of structurally diverse secondary metabolites, including compounds with antibacterial and antifungal activities. Several extracts and characterized metabolites have shown activity against microorganisms relevant to food safety and spoilage, yet their potential use in food biopreservation remains poorly resolved. This structured narrative review examines the antimicrobial evidence available for marine sponge-associated Actinobacteria and evaluates how closely that evidence approaches practical food application. Current studies range from antimicrobial screening of isolates and crude extracts to metabolomic characterization and direct testing of purified compounds. Activity has been reported against food-relevant microorganisms including pathogenic *Escherichia coli*, *Salmonella enterica*, *Bacillus cereus*, *Staphylococcus aureus*, and selected postharvest fungi. However, most investigations remain concentrated at the discovery and *in Vitro* bioactivity stages, with limited validation under preservation-relevant food conditions. Important uncertainties remain regarding efficacy in complex food matrices, stability during processing and storage, food-use safety, sensory compatibility, scalable production, and regulatory suitability. Future development should therefore focus on a smaller number of well-characterized candidates and progress them through quantitative antimicrobial validation, food-relevant target testing, matrix-specific challenge studies, safety and sensory assessment, and food-grade production. Marine sponge-associated actinobacterial metabolites consequently represent credible antimicrobial candidates for further food-oriented investigation, but their value for biopreservation will depend on translational validation rather than antimicrobial activity alone.

Keywords: Actinobacteria, antimicrobial metabolites, food biopreservation, foodborne pathogens, marine sponges, natural antimicrobials

Introduction

Control of pathogenic and spoilage microorganisms remains a fundamental objective of food preservation. However, antimicrobial activity measured under simplified laboratory conditions does not necessarily predict performance in a food product. Food composition and physicochemical conditions can substantially alter antimicrobial efficacy. In milk-based products, for example, the amount of nisin required for microbial control has been shown to vary with fat content, antimicrobial concentration, storage temperature, and the microorganism being targeted (Oshima *et al*., 2014) [20]. Similar matrix-dependent effects have been reported for *Listeria monocytogenes* in cheese models, where pH, temperature, and strain characteristics influenced sensitivity to nisin (Henderson *et al*., 2020) [11]. These observations highlight a basic distinction in the development of new food antimicrobials: promising *in Vitro* activity is useful for screening, but it is not evidence of preservative efficacy in food.

Actinobacteria are well known for producing structurally diverse secondary metabolites, many of which possess antimicrobial activity. Marine environments extend this biosynthetic diversity by providing ecological niches that differ from terrestrial systems, and marine sponges have repeatedly yielded cultivable Actinobacteria with considerable metabolic potential. Abdelmohsen *et al*. (2010) [1], for instance, recovered 90 actinomycete isolates representing 18 genera from 11 marine sponge species, several of which showed anti-infective activity. More recently, Fonseca *et al*. (2025) [9] isolated 79 Actinomycetota strains representing 12 genera from *Hymeniacidon perlevis*, including numerous *Streptomyces* isolates and several strains with antimicrobial activity. Such findings support marine sponges as useful reservoirs of chemically productive Actinobacteria. At the same time, the term "sponge-associated" needs to be used with care because recovery from sponge tissue does not by itself establish an obligate or host-specific symbiosis.

Evidence for antimicrobial production extends well beyond isolate-level screening. Viegelmann *et al*. (2014) [27], working with *Streptomyces* sp. SM8 from *Haliclona simulans*, combined metabolomic and genomic analyses to connect specific metabolites and biosynthetic machinery with antibacterial and antifungal activity. Compound-level evidence has also been reported for sponge-derived *Streptomyces* sp. G248, from which lavandulylated flavonoids were isolated and tested against microorganisms including *Bacillus cereus*, *Escherichia coli*, *Salmonella enterica*, and *Staphylococcus aureus* (Cao *et al*., 2019) [3]. The antimicrobial potential of sponge-associated Actinobacteria is therefore supported by evidence ranging from active extracts to chemically characterized compounds rather than by crude sponge bioactivity alone.

What remains less clear is how far this antimicrobial diversity can be translated into food preservation. Inhibition of a microorganism associated with foodborne disease or spoilage does not establish efficacy as a food biopreservative. The outcome may change with the strain used, antimicrobial concentration, assay system, food composition, processing conditions, and storage

environment. Evidence approaching application is still limited. Antimycin I from sponge-associated *Streptomyces* sp. NBU3104 is a notable example because it showed antifungal activity against *Penicillium expansum* and *Botrytis cinerea* and was subsequently evaluated for control of gray mold on apple fruit (Li *et al*., 2022) [17]. Even so, the study was developed primarily as an agricultural antifungal investigation rather than a comprehensive food-preservation assessment. Questions concerning food-matrix efficacy, physicochemical stability, toxicological safety, sensory compatibility, production scalability, and regulatory suitability therefore remain unresolved.

This structured narrative review examines antimicrobial metabolites from marine sponge-associated Actinobacteria from a food-science perspective. It considers how the evidence progresses from antimicrobial isolates and crude extracts to characterized metabolites, evaluates reported activity against microorganisms relevant to food safety and spoilage, and distinguishes antimicrobial potential from evidence that directly supports food preservation. Particular attention is given to the gap between compound discovery and practical biopreservation, including performance in food matrices, stability, safety, sensory acceptability, production feasibility, and regulatory readiness. The aim is not to catalogue marine natural products exhaustively, but to assess how far the current evidence has progressed toward credible food-biopreservation applications and to identify the research priorities needed to advance the most promising candidates.

Review Approach

This article was developed as a structured narrative literature review focused on the antimicrobial evidence reported for marine sponge-associated Actinobacteria and its relevance to food biopreservation. Literature identification concentrated mainly on peer-reviewed studies published from January 2000 to August 2026, while earlier publications were retained selectively when they provided important foundational evidence. Searches focused on PubMed-indexed literature and were supplemented by targeted searches of journal and publisher websites and citation-based discovery from relevant primary studies and their reference lists. Search concepts combined terms relating to marine sponges, including “marine sponge,” “sponge-associated,” and “sponge-derived”; Actinobacteria, including “Actinobacteria,” “Actinomycetota,” “actinomycetes,” and relevant genera such as *Streptomyces*, *Micromonospora,* and *Nocardiopsis*; and antimicrobial properties, including “antimicrobial,” “antibacterial,” “antifungal,” “secondary metabolite,” and “natural product.” Food-oriented searches additionally incorporated terms such as “foodborne,” “food spoilage,” “biopreservation,” “food matrix,” “preservative,” and “shelf life.”

The literature was considered through two complementary evidence streams. The first comprised core studies describing antimicrobial activity or antimicrobial metabolites from Actinobacteria isolated from, or clearly associated with, marine sponges. Priority was given to original studies in which the actinobacterial producer and sponge source were identifiable and in which antimicrobial assays, characterized extracts or metabolites, quantitative activity where available, and clearly defined test microorganisms were reported. The second stream addressed translation to food science. It included studies involving foodborne or spoilage microorganisms and literature used to define requirements for an effective food antimicrobial, such as matrix-dependent efficacy, physicochemical stability, toxicological safety, sensory compatibility, production feasibility, and regulatory assessment. Studies on non-sponge marine Actinobacteria or other microbial antimicrobial systems were used only for contextual or comparative purposes.

Studies were not treated as core evidence when antimicrobial activity could not be attributed to an actinobacterial producer, when only crude sponge extracts were tested without evidence of microbial origin, or when the reported activity was unrelated to antimicrobial effects. Research focused exclusively on anticancer, antiviral, antiparasitic, or other pharmacological activities was therefore excluded from the core antimicrobial evidence, although selected studies were retained when they provided relevant information on biosynthetic diversity, safety, or methodological considerations. Non-peer-reviewed or non-traceable sources were generally avoided when more reliable scientific sources were available.

Because the literature differed substantially in microbial sources, extraction procedures, compound characterization, test organisms, assay methods, and antimicrobial endpoints, the evidence was synthesized thematically rather than quantitatively. A six-level translational continuum was used to distinguish antimicrobial discovery from practical food relevance: identification of a sponge-associated actinobacterial source (L1); antimicrobial activity of an isolate, extract, or fraction (L2); characterized compound-level antimicrobial evidence (L3); evaluation under food-relevant or commodity-level conditions (L4); validation in an actual or model food system under preservation-relevant conditions (L5); and evidence supporting application readiness, including safety, sensory acceptability, scalable production, and regulatory suitability (L6). The continuum was developed for the present review as an analytical framework and is not intended as a standardized or validated assessment scale.

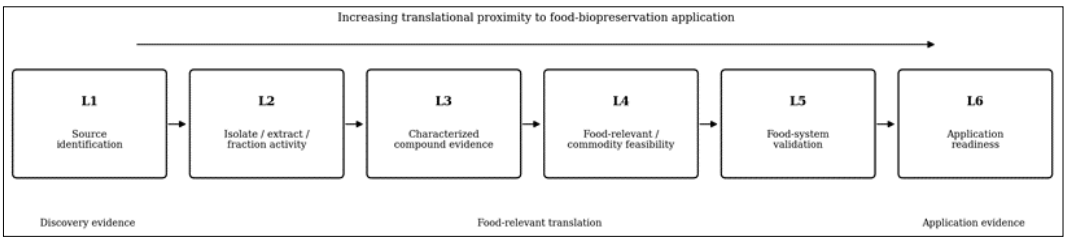

Fig 1: Discovery-to-biopreservation evidence continuum used to classify the proximity of current evidence to food application. L1-L6 are analytical levels proposed in this review, not a standardized readiness scale.

Marine Sponge-Associated Actinobacteria as Biosynthetic Reservoirs

Sponge–Actinobacteria Associations

Marine sponges host diverse microbial communities and have repeatedly yielded cultivable Actinobacteria, providing a clear biological basis for their investigation as sources of secondary metabolites. Culture-dependent studies have recovered substantial actinobacterial diversity from different sponge hosts and geographic regions. Zhang *et al*. (2006) [30], for example, isolated 106 Actinobacteria representing seven genera from *Hymeniacidon perleve*. Abdelmohsen *et al*. (2010) [1] subsequently recovered 90 actinomycetes affiliated with 18 genera from 11 sponge species collected in Egypt and Croatia. The association continues to be documented in more recent work: Fonseca *et al*. (2025) [9] obtained 79 Actinomycetota isolates belonging to 12 genera from *Hymeniacidon perlevis* collected along the Portuguese coast.

These studies establish marine sponges as reliable sources of cultivable Actinobacteria, but they do not justify treating every recovered strain as a host-specific symbiont. Community composition can also be influenced by cultivation methods, environmental exposure, and the ecological history of the host. Abdelmohsen *et al*. (2010) [1], for instance, found little evidence for broadly defined sponge-specific actinobacterial clades among the isolates examined. For this reason, "sponge-associated" is the more appropriate general term unless a closer symbiotic relationship has been demonstrated.

Taxonomic Diversity Relevant to Antimicrobial Discovery

Although *Streptomyces* is prominent in many cultivation-based studies, the actinobacterial diversity associated with marine sponges extends considerably beyond this genus. Xi *et al*. (2012) [28] isolated 327 strains from eight sponges collected from the South China Sea and Yellow Sea and identified representatives of 13 genera among the isolates selected for phylogenetic analysis. *Micromonospora* and *Streptomyces* were particularly prominent. Other studies have recovered genera such as *Nocardiopsis, Nocardia, Rhodococcus,* and *Gordonia*. Fonseca *et al*. (2025) [9] likewise identified 12 Actinomycetota genera, although all 13 isolates showing antimicrobial activity in that study belonged to *Streptomyces*.

The repeated recovery of *Streptomyces* helps explain its dominant position in the antimicrobial literature, but it should not obscure the wider actinobacterial reservoir. At the same time, comparisons among surveys require caution because differences in medium composition and isolation procedures affect which members of a community can be cultured. The apparent dominance of a genus in a culture collection therefore need not mirror its true ecological abundance within the sponge.

Biosynthetic Capacity and Metabolite Production

Taxonomic diversity is accompanied by substantial biosynthetic potential. In the China Seas survey, 27.5% of the actinobacterial isolates examined showed antimicrobial activity, whereas polyketide synthase (PKS) and/or nonribosomal peptide synthetase (NRPS) genes were detected in 91% of the isolates screened (Xi *et al*., 2012) [28]. The difference is informative. It suggests that biosynthetic capacity can exceed the antimicrobial phenotype expressed under a particular cultivation and assay condition. At the same time, the presence of a PKS or NRPS marker does not prove production of the corresponding metabolite or establish that the product is antimicrobial.

Metagenomic work points in the same direction. Pimentel-Elardo *et al*. (2012) [21] identified diverse NRPS sequences in marine sponge microbiomes, including lineages predicted to have actinobacterial affiliations. Such findings indicate that cultivation-based surveys capture only part of the biosynthetic diversity present within sponge-associated microbial communities.

Metabolite expression can also change substantially with culture conditions. Shamikh *et al*. (2020) [23] showed that co-cultivation of sponge-derived *Micromonospora* sp. UA17 with mycolic-acid-containing Actinobacteria, or supplementation with mycolic acid, altered the metabolite profile and revealed compounds that were not detected under the corresponding monoculture conditions. This type of response suggests that screening a strain under a single laboratory condition may underestimate its chemical capacity.

More direct attribution has been achieved for *Streptomyces* sp. SM8 from *Haliclona simulans*. Viegelmann *et al*. (2014) [27] combined metabolomic and genomic analyses to identify antibacterial fractions containing hydroxylated saturated fatty acids and to associate antifungal activity with antimycin production. Disruption of the antimycin biosynthetic gene *antC* eliminated detectable antimycin production and markedly reduced antifungal activity. The study therefore linked genetic potential, metabolite production, and biological activity more convincingly than metabolite detection alone. Overall, the literature establishes considerable taxonomic and biosynthetic potential among sponge-associated Actinobacteria, while also showing that genetic potential, metabolite expression, and demonstrated antimicrobial activity represent different levels of evidence.

Antimicrobial Metabolites from Sponge-Associated Actinobacteria

From Isolate-Level Activity to Compound-Level Evidence

Antimicrobial studies on sponge-associated Actinobacteria vary widely in the degree to which the active substance has been characterized. At the most preliminary level, inhibition may be demonstrated for a strain or crude culture extract without identifying the molecules responsible. Chemical profiling can narrow the possibilities by showing which metabolites are present in an active extract, but detection by GC-MS, LC-MS, or related methods does not establish that every detected compound contributes to the antimicrobial effect. Stronger attribution is obtained when the active constituent is purified and tested directly, and it can be strengthened further when genomic or functional evidence connects the compound to its microbial producer.

Selvin *et al*. (2009) [22] provide an early example of extract-level evidence. *Nocardiopsis dassonvillei* MAD08, isolated from *Dendrilla nigra*, produced an ethyl-acetate extract with activity against the multidrug-resistant pathogens used in the study. Chemical analysis of an active chromatographic fraction suggested several constituent compounds, while a water-soluble anticandidal protein was recovered separately from the culture supernatant. The work established that this sponge-associated Actinobacterium produced chemically distinct antimicrobial materials, but the organic extract was

not resolved into individual purified compounds whose activities were confirmed separately.

A similar distinction is important when interpreting more recent Indonesian studies. Efendi *et al*. (2025) [4] reported that an ethyl-acetate extract of *Streptomyces* sp. Dbi28t inhibited an ESBL-producing *E. coli* strain as well as *Providencia rettgeri*, *Proteus mirabilis*, and *Pseudomonas putida*. LC-MS/MS detected nine major metabolites in the active extract, including pumilacidins, surfactins, phenazostatin B, chalcomycin B, neopyrrolomycin C, saquayamycin A, and saphenamycin. Because the antibacterial assay was performed with the extract rather than the purified metabolites, the compounds are more appropriately regarded as constituents associated with an active extract than as independently confirmed antibacterial agents in that experiment.

The same caution applies to *Streptomyces tendae* Cal24h associated with *Callyspongia* sp. Larasati *et al*. (2025) [16] reported inhibition of enteropathogenic *E. coli* K1.1, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and methicillin-resistant *Staphylococcus aureus*. The optimized extract produced inhibition zones of approximately 18.6–20.5 mm, with MIC values of 62.5–125 µg/mL. GC-MS and LC-MS profiling detected several diketopiperazines, including cyclo (Leu-Pro), cyclo(L-Pro-L-Val), and cyclo (Pro-Phe). These results associate the chemical profile with antibacterial activity but do not establish the contribution of each detected diketopiperazine.

Characterized Antibacterial Metabolites

More informative evidence is available when bioassay-guided isolation connects activity with a defined molecule. Huang *et al*. (2019) [13] investigated sponge-derived strain HNM0039T, subsequently described as *Streptomyces tirandamycinicus*. Bioassay-guided fractionation yielded tirandamycins A and B, which showed MIC values of 2.52 and 2.55 µg/mL against *Streptococcus agalactiae*, respectively. Activity was also reported against *B. subtilis*, whereas the compounds were inactive against the tested *S. aureus* and *E. coli* strains at 128 µg/mL. The selective spectrum is important because it shows why a compound cannot be assumed to have broad antimicrobial utility simply because it performs strongly against one target.

A particularly relevant example for food-oriented interpretation is *Streptomyces* sp. G248 from *Halichondria panicea*. Cao *et al*. (2019) [3] isolated three new lavandulylated flavonoids together with seven known metabolites and tested the purified compounds against a microbial panel that included *Enterococcus faecalis*, *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella enterica*. Several of these species are relevant to food safety. The study therefore provides a useful connection between marine natural-product discovery and food microbiology, although all activity was measured under laboratory conditions rather than in food.

Compound-level antimicrobial evidence is not restricted to *Streptomyces*. Matroodi *et al*. (2020) [19] isolated *Streptomonospora* sp. PA3 from a Persian Gulf sponge and purified the new aromatic polyketide persiamycin A. Direct agar-diffusion testing showed moderate inhibition of *S. aureus*, *Klebsiella pneumoniae*, and *P. aeruginosa*. Although quantitative MIC values were not reported, the work remains informative because biological activity was evaluated using the purified compound rather than inferred from a complex extract.

Antifungal Metabolites and Broader Antimicrobial Spectra

Antifungal activity broadens the potential relevance of sponge-associated Actinobacteria beyond bacterial pathogen control and creates a clearer link with postharvest deterioration. The work on *Streptomyces* sp. SM8 is particularly instructive because Viegelmann *et al*. (2014) [27] combined metabolomic, genomic, and functional evidence. Hydroxylated saturated fatty acids were associated with antibacterial fractions, whereas antimycins were linked to antifungal activity. Disruption of *antC* eliminated detectable antimycin production and substantially reduced the antifungal phenotype, providing stronger producer–metabolite–activity attribution than chemical profiling alone.

A more application-proximal case was reported for sponge-associated *Streptomyces* sp. NBU3104. Li *et al*. (2022) [17] isolated eight new antimycin analogues, designated antimycins I–P. Antimycin I inhibited a fungal panel that included *Candida albicans*, *Penicillium expansum*, *P. citrinum*, and *Botrytis cinerea* and was subsequently tested against gray mold on apple fruit. With an MIC of 8 µg/mL and demonstrated suppression of gray mold *in vivo*, the study represents the closest approach to commodity-level application among the examples identified in this review. Its purpose, however, was agricultural antifungal development rather than comprehensive food-preservation validation, so the result should not be interpreted as evidence of established food-biopreservation efficacy.

Potency, Assay Heterogeneity, and Evidence Comparability

Numerical antimicrobial results across these studies are not directly interchangeable. Investigations differ in whether they test whole isolates, crude extracts, fractions, or purified compounds, as well as in microbial strain, inoculum, medium, solvent, concentration, and assay format. A large inhibition zone obtained with an extract therefore cannot be interpreted as stronger evidence than a lower MIC for a purified compound without considering the experimental context. For example, the 62.5–125 µg/mL MIC range reported for the Cal24h extract cannot be compared directly with the approximately 2.5 µg/mL MIC values of purified tirandamycins against *S. agalactiae* because neither the antimicrobial material nor the target organism is equivalent.

Chemical attribution requires the same caution. Detection of a metabolite in an active extract strengthens characterization but does not establish causality. Bioassay-guided purification, direct testing of isolated compounds, or functional interruption of a biosynthetic pathway provides stronger evidence. The literature therefore forms a continuum from preliminary screening to well-characterized compound-level activity rather than a uniform body of equivalent antimicrobial results. For food-oriented development, candidates should be prioritized not only because activity has been observed, but because the active substance is sufficiently defined and its effect can be reproduced quantitatively under controlled conditions.

Table 1: Representative antimicrobial evidence reported for marine sponge-associated Actinobacteria

Sponge host/source	Actinobacterial producer	Active material	Attribution basis	Representative target(s)	Quantitative/main evidence	Food relevance	Evidence level	Reference
Dendrilla nigra	*Nocardiopsis dassonvillei* MAD08	Ethyl-acetate extract and active fraction	Active extract + chemical profiling	MDR bacterial pathogens; *Candida* spp.	Broad extract activity; active fraction chemically profiled; preliminary non-hemolytic evidence	Indirect	L2	Selvin *et al.* (2009) [22]
Marine sponge isolates, Seribu Islands	*Streptomyces* sp. Dbi28t	Ethyl-acetate extract	Active extract + LC-MS/MS metabolite annotation	ESBL-producing *E. coli*, *P. rettgeri*, *P. mirabilis*, *P. putida*	Antibacterial inhibition; nine major metabolites detected in active extract	Indirect food-safety relevance through *E. coli*	L2	Efendi *et al.* (2025) [4]
Callyspongia sp.	*Streptomyces tendae* Cal24h	Ethyl-acetate extract	Active extract + GC-MS/LC-MS profiling	EPEC *E. coli*, *P. aeruginosa*, *B. subtilis*, MRSA	Inhibition zones 18.57–20.54 mm; extract MIC 62.5–125 μg/mL	Strong indirect relevance for EPEC	L2	Larasati *et al.* (2025) [16]
Marine sponge	*Streptomyces tirandamycinicus* HNM0039T	Tirandamycins A and B	Bioassay-guided purification + direct compound testing	*S. agalactiae*, *B. subtilis*	MIC 2.52/2.55 μg/mL against *S. agalactiae*; 5.5/6.8 μg/mL against *B. subtilis*	Mainly aquaculture/peripheral	L3	Huang *et al.* (2019) [13]
Halichondria panicea	*Streptomyces* sp. G248	Lavandulylated flavonoids	Purified compounds + direct antimicrobial testing	*B. cereus*, *E. coli*, *S. enterica*, *S. aureus* and others	Purified compounds displayed antimicrobial activity; one compound showed broader activity across the tested panel	Strong indirect food-safety relevance	L3	Cao *et al.* (2019) [3]
Persian Gulf sponge	*Streptomonospora* sp. PA3	Persiamycin A	Purified compound + direct agar-diffusion assay	*S. aureus*, *K. pneumoniae*, *P. aeruginosa*	Moderate inhibition by purified compound	Partial/indirect	L3	Matroodi *et al.* (2020) [19]
Haliclona simulans	*Streptomyces* sp. SM8	Antimycins; antibacterial fatty-acid-containing fractions	Metabolomics + genomic evidence + biosynthetic-gene disruption	Bacterial and fungal test organisms	Loss of antimycin production and reduced antifungal activity following *antC* disruption	Indirect	L3	Viegelman n *et al.* (2014) [27]
Marine sponge	*Streptomyces* sp. NBU3104	Antimycin I	Purified compound + direct antifungal assay + apple experiment	*P. expansum*, *P. citrinum*, *B. cinerea*	MIC 8 μg/mL; control of gray mold on apple *in vivo*	Commodity-level/postharvest relevance	L4	Li *et al.* (2022) [17]

Note: Evidence levels are analytical categories developed for this review; they are not a standardized scoring system.

Relevance of the Antimicrobial Evidence to Food Safety

Evidence Against Foodborne Pathogens

Several microorganisms used in sponge-associated actinobacterial studies are established foodborne pathogens, giving the antimicrobial evidence a legitimate food-safety dimension (FDA, 2012) [25]. Yet species identity alone is not enough to establish direct food relevance. Natural-product studies are often designed around pharmaceutical or antimicrobial-resistance questions, and the strains used may be reference cultures or clinical isolates rather than organisms obtained from food.

The purified flavonoids from *Streptomyces* sp. G248 provide one of the clearest compound-level links with food-relevant bacterial targets. Cao *et al*. (2019) [3] tested the compounds against defined ATCC strains of *B. cereus*, *E. coli*, *Salmonella enterica*, and *S. aureus*, together with several other microorganisms. This constitutes strong evidence of activity against species associated with foodborne illness, but it remains indirect from the standpoint of preservation because the experiments used laboratory cultures rather than food-derived strains or food matrices.

The distinction is even more important for Dbi28t. Its ethyl-acetate extract inhibited an ESBL-producing *E. coli* strain, but the strain originated from a hospital patient rectal swab (Efendi *et al*., 2025) [4]. The experiment therefore demonstrates activity against a clinically derived antimicrobial-resistant *E. coli*, not against an isolate recovered from food. Pathogenic *E. coli* is clearly important

to food safety, but the Dbi28t study supports relevance at the species level rather than direct evidence of foodborne control.

S. tendae Cal24h provides a closer etiological link because it was tested against EPEC *E. coli* K1.1 (Larasati *et al*., 2025) [16]. The EPEC strain originated from a university microbial collection, while the remaining organisms were obtained from a microbiology laboratory; the article does not identify them as food isolates. The extract inhibited all four targets, with MIC values of 62.5–125 μg/mL and MBC values above 250 μg/mL. EPEC gives the result meaningful food-safety relevance, but the evidence remains at the *in Vitro* extract level.

An emerging example involving a seafood-relevant pathogen comes from sponge-derived *Streptomyces variabilis*. Its extract was evaluated in a *Caenorhabditis elegans–Vibrio parahaemolyticus* infection model and improved host survival (Acosta *et al*., 2026) [2]. This takes the work beyond a conventional inhibition assay, but it still does not establish control of *V. parahaemolyticus* in fish or shellfish. The case illustrates how biological relevance to a foodborne pathogen can increase while the experimental system remains distant from a preservation application.

Some important foodborne pathogens remain less visible in the mapped sponge-associated actinobacterial literature. *Listeria monocytogenes*, in particular, was not prominent among the core studies identified. This should not be interpreted as evidence that the organism has never been investigated, but it suggests that targeted screening against *Listeria* and other application-specific foodborne organisms deserves greater attention.

Food Spoilage and Postharvest Organisms

The food relevance of sponge-associated actinobacterial metabolites also extends to spoilage and postharvest deterioration. Antimycin I from *Streptomyces* sp. NBU3104 is the strongest example identified. The purified compound inhibited *P. expansum, P. citrinum,* and *B. cinerea*, among other fungi, and subsequently controlled gray mold on apple fruit *in vivo* (Li *et al*., 2022) [17].

Activity against *P. expansum* is noteworthy because the organism is an important postharvest pathogen of pome fruits and is capable of producing the mycotoxin patulin (Tragni *et al*., 2021) [24]. Its control may therefore have implications for both product quality and food safety. *B. cinerea* is better interpreted primarily as a postharvest decay and plant-disease target rather than a classical foodborne pathogen. Keeping these functions separate is useful because microbial preservation encompasses both reduction of food-safety hazards and control of deterioration, but the endpoints needed to demonstrate each benefit are not identical.

The apple experiment with antimycin I is best regarded as commodity-level postharvest validation. It shows that antimicrobial activity can persist beyond laboratory culture and operate on an actual harvested commodity. A preservation-oriented assessment, however, would need to address a broader set of outcomes, including microbial behavior during storage, effects on product quality, compound stability and residues, toxicological implications, and, where relevant, sensory acceptability.

From Pathogen Relevance to Food-Preservation Evidence

Food relevance is therefore better viewed as a continuum than as a binary property. Activity against a species associated with foodborne disease creates an initial connection with food safety, but stronger evidence requires progressively closer correspondence with the intended application. This may involve testing foodborne or food-derived strains, demonstrating activity under relevant physicochemical conditions, validating efficacy in a model or actual food matrix, and ultimately showing preservation benefits without unacceptable effects on product quality or safety.

Most sponge-associated actinobacterial studies identified here remain toward the earlier part of this continuum. G248 provides strong compound-level evidence against several food-relevant species, Dbi28t and Cal24h demonstrate activity against pathogenic *E. coli* at the extract level, and the *S. variabilis–V. parahaemolyticus* work extends evaluation into an infection model. Antimycin I from NBU3104 comes closest to commodity-level application through its direct evaluation on apple fruit. Taken together, the literature establishes genuine food relevance, but validated food-biopreservation evidence remains considerably less developed than antimicrobial discovery.

Table 2: Food relevance and translational status of representative antimicrobial evidence from marine sponge-associated Actinobacteria

Target microorganism	Test-strain/context	Producer or active material	Food relevance	Evidence type	Food matrix tested?	Translational interpretation	Reference
Bacillus cereus ATCC 13245	Reference laboratory strain	Purified flavonoids from *Streptomyces* sp. G248	Strong indirect food-safety relevance	Purified compound assay	No	Recognized foodborne species, but evidence remains laboratory-based	Cao *et al*. (2019) [3]
Salmonella enterica ATCC 12228	Reference laboratory strain	Purified flavonoids from *Streptomyces* sp. G248	Strong indirect food-safety relevance	Purified compound assay	No	Strong compound attribution without food-derived strain or food-matrix validation	Cao *et al*. (2019) [3]
Escherichia coli ATCC 25922	Reference laboratory strain	Purified flavonoids from *Streptomyces* sp. G248	Indirect food-safety relevance	Purified compound assay	No	Food-relevant species; foodborne pathotype and matrix were not evaluated	Cao *et al*. (2019) [3]
Staphylococcus aureus ATCC 25923	Reference laboratory strain	Purified flavonoids from *Streptomyces* sp. G248	Strong indirect food-safety relevance	Purified compound assay	No	Relevant foodborne species; no preservation validation	Cao *et al*. (2019) [3]

ESBL-producing *E. coli*	Clinical isolate from hospital-patient rectal swab	Ethyl-acetate extract of *Streptomyces* sp. Dbi28t	Moderate indirect relevance	Active extract + LC-MS/MS profiling	No	Clinically derived resistant strain; food relevance occurs at species level rather than through food origin	Efendi *et al*. (2025) [4]
EPEC *E. coli* K1.1	University microbial collection; food origin not stated	Ethyl-acetate extract of *S. tendae* Cal24h	Strong indirect relevance	Extract-level MIC/MBC + metabolite profiling	No	Relevant pathogenic enteric strain, but without food-matrix validation	Larasati *et al*. (2025) [16]
Vibrio parahaemolyticus	*C. elegans* infection model	Sponge-derived *Streptomyces variabilis* extract	Strong seafood-safety target relevance but indirect application evidence	Extract tested in biological infection model	No	Extends beyond simple *in Vitro* screening but not to seafood preservation	Acosta *et al*. (2026) [2]
Penicillium expansum	Postharvest fungal target	Purified antimycin I from *Streptomyces* sp. NBU3104	Strong postharvest and potential food-safety relevance	Purified compound antifungal assay	No	Relevant to postharvest decay and patulin risk; the study did not demonstrate preservation efficacy or patulin reduction against *P. expansum* in apple	Li *et al*. (2022) [17]
Botrytis cinerea	Postharvest plant-pathogenic fungus	Purified antimycin I from *Streptomyces* sp. NBU3104	Commodity/postharvest relevance	Purified compound + apple in-*vivo* assay	Yes — apple	Strongest commodity-level translation identified, but not comprehensive food-biopreservation validation	Li *et al*. (2022) [17]
Penicillium citrinum	Filamentous fungal target	Purified antimycin I from *Streptomyces* sp. NBU3104	Spoilage-related indirect relevance	Purified compound assay	No	Antifungal relevance demonstrated; food application not evaluated	Li *et al*. (2022) [17]

Note: Food-relevance classifications were developed for this review to indicate proximity to food-safety or preservation applications and were not assigned by the original authors.

Translational Requirements for Food Biopreservation Performance in Food Matrices

Activity measured in agar or broth cannot be assumed to persist unchanged in food. Proteins, lipids, salts, endogenous enzymes, pH, water activity, competing microbiota, and storage temperature can all alter antimicrobial availability and efficacy. Work with established biopreservation systems illustrates this matrix dependence. Oshima *et al*. (2014) [20], for example, found that the amount of nisin A required for microbial control in chilled milk pudding varied with fat content, target organism, antimicrobial concentration, and storage temperature. More recent studies have advanced further by testing antimicrobial candidates directly in defined food systems; Geng *et al*. (2026) [10], for instance, evaluated bacteriocin LL4 against *Salmonella Typhimurium* in refrigerated simulated milk.

Comparable matrix-level evidence is still uncommon for sponge-associated actinobacterial metabolites. Purified compounds such as the G248 flavonoids and tirandamycins have been characterized under laboratory conditions but not validated in food. Antimycin I from NBU3104 is an important exception because its activity was evaluated on apple fruit, although the experiment focused on gray-mold control rather than a comprehensive preservation assessment. Future studies should therefore select food matrices according to antimicrobial spectrum and intended use and determine whether meaningful microbial control can be achieved at technologically realistic concentrations under relevant processing and storage conditions.

Stability During Processing and Storage

A candidate biopreservative must retain sufficient activity during manufacture, incorporation into food, storage, and use. The relevant stability requirements will depend on the intended application and may include resistance to heat, acidic or neutral pH, salinity, enzymes, oxidation, or prolonged storage. Food-oriented antimicrobial research shows why these factors should be examined before practical suitability is inferred. The antimicrobial peptide NP-6, for example, retained activity after heating under several conditions but lost activity in the presence of some divalent ions and after exposure to trypsin or proteinase K (Hou *et al*., 2019) [12].

Comparable physicochemical data remain limited for the sponge-associated candidates mapped in this review. Most studies have concentrated on microbial cultivation, metabolite production, extraction, or antimicrobial potency rather than the stability of purified compounds under food-processing conditions. Testing should therefore be tailored to the intended product. Heat stability may matter most for compounds added before thermal processing, whereas low-temperature activity and salt tolerance may be more important for refrigerated seafood. In protein-rich foods, binding interactions or enzymatic degradation may become more limiting than heat exposure itself.

Safety and Toxicological Requirements

Food-use safety must be established independently of antimicrobial efficacy. A compound is not safe for ingestion simply because it is natural or produced by a marine microorganism. Regulatory assessment similarly considers identity, intended use, exposure, manufacturing process, and toxicological information rather than source alone.

Safety information within the sponge-associated antimicrobial literature remains preliminary. Selvin *et al*. (2009) [22], for instance, reported that the active material

produced by *N. dassonvillei* MAD08 was non-hemolytic. This is useful as an early biological observation but cannot establish oral or chronic safety, genotoxicity, or an acceptable level of dietary exposure.

Experience with other *Streptomyces*-derived products used in the food chain illustrates the broader evidence that may eventually be required. In an EFSA assessment of collagenase produced by *Streptomyces violaceoruber*, evaluation included characterization of the production organism, absence of viable cells and DNA, genotoxicity, repeated-dose oral toxicity, dietary exposure, and allergenicity before a safety conclusion was reached under the specified conditions of use (EFSA CEP Panel, 2024) [6]. The importance of evidence completeness is also illustrated by AMP deaminase produced by *Streptomyces murinus*. An assessment in 2023 could not conclude on safety because the commercial and toxicological batches had not been adequately characterized, whereas an updated assessment incorporating additional data in 2025 concluded that the enzyme did not raise safety concerns under its intended conditions of use (EFSA CEP Panel, 2023; EFSA FEZ Panel, 2025) [5, 7].

The antimycin example deserves particular caution. Antimycin I from NBU3104 showed promising antifungal efficacy, but related antimycin chemistry includes compounds with strong biological effects in eukaryotic systems. Antimycin A, for example, is a well-established inhibitor of mitochondrial complex III (Lai *et al*., 2005) [15]. This does not establish that antimycin I has the same toxicological profile, and it would be inappropriate to label antimycin I unsafe on that basis. It does, however, make compound-specific toxicological evaluation essential before food use can be considered.

Sensory Compatibility and Effective Concentration

Microbiological efficacy alone does not ensure technological suitability. An antimicrobial may perform well against a target organism yet be unusable if the required concentration causes unacceptable taste, aroma, color, or textural changes. Effective concentration and sensory acceptability therefore need to be considered together.

More advanced food-biopreservation studies routinely examine microbial and quality outcomes in parallel. Kondrotienė *et al*. (2019) [14], for example, evaluated fresh cheese made with nisin Z-producing *Lactococcus lactis* for pathogen control as well as acidity, volatile compounds, flavor intensity, color, bitterness, and crumbliness during storage. Oshima *et al*. (2014) [20] likewise integrated microbiological control with aroma and organoleptic evaluation in milk pudding.

Comparable sensory evidence was not prominent among the sponge-associated actinobacterial studies examined here. This gap matters because a compound with a favorable MIC may still fail as a preservative if its effective use level exceeds a sensory or technological threshold. Early food-system studies should therefore examine whether antimicrobial efficacy can be achieved while maintaining the characteristics expected of the intended product.

Production, Recovery, and Scalability

Production optimization has received more attention than food-matrix or sensory validation. Selvin *et al*. (2009) [22] optimized submerged fermentation conditions for antimicrobial production by *N. dassonvillei* MAD08. Efendi *et al*. (2025) [4] reported improved antibacterial production by sponge-associated *Streptomyces* under modified molasses medium and a 15-day incubation period, while Larasati *et al*. (2025) [16] found modified A1 medium to provide the highest extract yield and strongest antibacterial activity for Cal24h among the media evaluated.

These studies show that metabolite production can be manipulated through cultivation conditions, but laboratory optimization is still far removed from industrial feasibility. Food-grade development would require reproducible yield, batch consistency, suitable fermentation substrates, efficient downstream recovery, purification where necessary, control of extraction solvents and other residues, formulation, and stability at larger scale. Products derived from microbial fermentation may also require attention to the production strain, residual viable cells or DNA, and potentially harmful metabolites. Current EFSA guidance for products containing, made from, or produced with microorganisms addresses characteristics including taxonomic identity, antimicrobial-resistance traits, toxigenicity or pathogenicity, and, where relevant, the presence of viable cells, DNA, or other substances of concern in the resulting product (EFSA Scientific Committee, 2025) [8].

Regulatory Readiness

Regulatory readiness lies at the end of the translational pathway rather than following automatically from antimicrobial activity. FDA guidance for antimicrobial agents used in food applications emphasizes evidence that the antimicrobial achieves its intended technical effect under the proposed conditions of use and that the intended use is safe (FDA, 2021) [26]. For microbial-derived antimicrobials, characteristics of the production organism, pathogenicity or toxigenicity, clinically relevant antimicrobial production, and the possible presence of viable production cells may also be relevant.

The eventual regulatory route for any sponge-associated actinobacterial metabolite would depend on jurisdiction, chemical identity, manufacturing process, intended function, proposed use level, and exposure. It would therefore be premature to assign GRAS, food-additive, processing-aid, or comparable regulatory status to any candidate reviewed here. Antimicrobial potency is only one component of the evidence needed to move from Levels 3–4 toward Levels 5–6; matrix-specific efficacy, stability, safety, sensory compatibility, manufacturing consistency, and a defined intended-use scenario would also be required.

Knowledge Gaps and Research Priorities

The main obstacle to progress is no longer simply a lack of bioactive isolates or candidate metabolites. Recent work continues to recover diverse sponge-associated Actinomycetota and to identify active extracts and previously unassigned metabolomic features. Fonseca *et al*. (2025) [9], for example, combined antimicrobial screening with mass-spectrometry-based dereplication and identified both known metabolites and molecular features without clear matches to characterized natural products. Discovery therefore remains productive. The more consequential question is which candidates can move beyond discovery and become reproducible, safe, and technically realistic options for food use.

Strengthening Compound Attribution and Antimicrobial Evidence

The first priority is to reduce reliance on crude-extract activity and tentative metabolite annotation. Screening extracts is useful for identifying productive strains, but development toward food application requires greater confidence regarding the substance responsible for the observed effect. Promising extracts should therefore progress through bioassay-guided fractionation, purification, structural confirmation, and direct testing of the isolated compound. Quantitative MIC and, when appropriate, MBC or MFC values should be supported by suitable controls and independent production batches.

Metabolomic dereplication can accelerate this process but cannot replace it. An annotated mass feature is not equivalent to a purified active metabolite, particularly in chemically complex extracts. Candidates should advance only when antimicrobial activity is reproducible and can be attributed with reasonable confidence to a defined compound or sufficiently characterized active fraction.

Expanding Food-Relevant Target Validation

The second priority is to align antimicrobial testing with the intended food application. Much of the current literature relies on reference strains, clinical pathogens, or broad screening panels. These choices establish biological activity but may provide little information about performance against the organisms most relevant to a particular food.

Future studies should therefore include multiple strains of priority foodborne or spoilage microorganisms and, where feasible, food-derived isolates. Target selection should follow the proposed application. The *S. variabilis–V. parahaemolyticus* study illustrates both progress and remaining distance: the pathogen is highly relevant to seafood safety, and evaluation progressed to an infection model, but no seafood matrix was tested (Acosta *et al*., 2026) [2]. The next meaningful step is not another unrelated bioassay but validation against the same or comparable target under seafood-relevant conditions.

Advancing from In *Vitro* Activity to Food-System Validation

Once a candidate has sufficient compound-level attribution and activity against an appropriate food-relevant target, it should progress to matrix-specific validation. Testing can move from relevant pH, salinity, temperature, and storage conditions to model foods and, finally, controlled challenge studies in the intended commodity. At this stage, preservation-related outcomes should be evaluated alongside microbial inhibition.

Food-antimicrobial research outside the sponge field provides useful benchmarks. Xu *et al*. (2026) [29] evaluated thanatin in chilled pork, lettuce, salmon, water, and chicken breast and measured both microbial reduction and quality changes during refrigerated storage. Li *et al*. (2026) [18] similarly characterized a stabilized cyclic temporin for resistance to pH, saline conditions, and proteolysis before testing it in *S. aureus*-inoculated pork. For sponge-associated actinobacterial metabolites, an equivalent level of evidence would require reproducible microbial control together with relevant quality outcomes under realistic storage conditions.

Integrating Safety and Sensory Acceptability Early in Development

Safety and acceptability should function as early development gates rather than late-stage formalities. The same biosynthetic diversity that makes sponge-associated Actinobacteria attractive for antimicrobial discovery can also generate compounds with unwanted biological effects. Potency must therefore be considered alongside an emerging safety profile.

Initial candidate triage should include appropriate preliminary safety assays and progress toward more relevant toxicological assessment as intended use and expected exposure become clearer. Sensory compatibility should be considered once safe food testing is justified. A compound that controls a target only at a concentration that produces unacceptable flavor, odor, color, or texture is unlikely to become a useful preservative regardless of its MIC.

This stage also provides a rational stopping point. Candidates showing unacceptable toxicity, persistent loss of activity under relevant conditions, or unacceptable product effects should not continue automatically because they represent chemically novel marine metabolites. Development resources are better directed toward candidates with a more balanced profile of efficacy, safety, stability, and acceptability.

Scaling Production and Building Application Readiness

The final priority is to connect laboratory metabolite production with reproducible food-grade manufacture. Culture optimization shows that antimicrobial yield can be manipulated, but application requires much more than obtaining an active laboratory extract. Selected candidates ultimately need reproducible fermentation yield, batch consistency, appropriate growth media, efficient downstream recovery, adequate purification, formulation, stability, and control of processing residues or other substances of concern.

The most appropriate development route will depend on the candidate. For many compounds, production of a chemically defined metabolite through controlled fermentation and purification may be more practical than adding a sponge-derived Actinobacterium directly to food. Other candidates may require formulation or delivery systems to maintain activity at acceptable use levels. These decisions should be made only after the intended food, concentration, exposure, and manufacturing process have been defined sufficiently to support safety and regulatory assessment.

Taken together, the evidence favors a stage-gated strategy rather than indiscriminate progression of every active isolate or metabolite. Development should move from reliable compound attribution and quantitative antimicrobial activity through food-target validation and matrix-specific challenge testing, followed by safety and sensory assessment and, finally, scalable production and regulatory evaluation. Advancement should remain conditional: failure to achieve adequate activity, safety, matrix stability, or product acceptability should lead to reformulation, modification, or discontinuation rather than automatic progression. Progress in this field will be more meaningful when measured by the number of candidates that successfully move toward credible food-biopreservation use than by the number of newly reported antimicrobial metabolites.

Table 3: Stage-gated research priorities for translating sponge-associated actinobacterial antimicrobials into food-biopreservation candidates

Research gate	Current evidence landscape	Critical question	Required next evidence	Proposed advancement criterion
Gate A — Candidate confirmation	Several purified compounds have been characterized, although many studies remain extract- or fraction-based	Can the antimicrobial effect be reproducibly attributed to a defined substance?	Bioassay-guided purification; structural confirmation; MIC/MBC/MFC where appropriate; batch reproducibility	Defined compound or sufficiently characterized fraction with reproducible antimicrobial activity
Gate B — Food-target validation	Several food-relevant species have been tested, but reference and clinical strains remain common	Does the candidate act against microorganisms relevant to its intended food application?	Multiple relevant strains; food-derived isolates where available; application-specific target panels	Reproducible activity against clearly relevant targets at technologically plausible concentrations
Gate C — Food-system validation	Direct food-matrix evidence remains uncommon; commodity-level evidence is limited	Does activity persist under realistic processing and storage conditions?	Stability testing; model food; actual food challenge studies; microbial and quality/shelf-life outcomes	Meaningful microbial control in the intended matrix without unacceptable loss of product quality
Gate D — Safety and acceptability	Food-use toxicological and sensory evidence remains sparse in the mapped sponge-associated literature	Is the effective exposure sufficiently safe and acceptable in the food?	Candidate-appropriate toxicological assessment; exposure estimation; sensory and physicochemical-quality testing	Adequate safety margin and acceptable product characteristics at the effective use level
Gate E — Application readiness	Laboratory cultivation and metabolite-production optimization exist, but food-grade manufacturing evidence remains limited	Can the candidate be produced, formulated, and used reproducibly at practical scale?	Reproducible fermentation; downstream recovery; purification/formulation; pilot validation; intended-use and regulatory assessment	Controllable food-grade manufacture and an intended use supported by sufficient efficacy and safety evidence

Note: The research gates and advancement criteria constitute a conceptual framework proposed in this review. They are not a validated technology-readiness or regulatory classification.

Conclusion

Marine sponge-associated Actinobacteria constitute a credible reservoir of antimicrobial metabolites with substantial structural and functional diversity. The available evidence ranges from active cultured isolates and crude extracts to chemically characterized compounds with measurable activity against bacterial and fungal targets. Some of these targets are relevant to food safety and spoilage, establishing a legitimate connection with food science rather than limiting the field to pharmaceutical natural-product discovery.

The evidence for antimicrobial discovery, however, remains considerably stronger than the evidence for food-biopreservation application. Activity against a food-relevant microorganism under laboratory conditions does not demonstrate preservative efficacy in a complex food system, and only limited work has progressed toward commodity-level evaluation. Important uncertainties remain around matrix performance, stability during processing and storage, food-use safety, sensory compatibility, reproducible production, downstream processing, and regulatory suitability. These limitations are especially important because biological potency and natural marine origin cannot be taken as evidence of suitability for food use.

Future development should therefore concentrate on carefully selected candidates rather than continued accumulation of antimicrobial compounds alone. Candidates with reliable compound attribution and reproducible antimicrobial activity should progress to testing against relevant foodborne or spoilage strains, validation under realistic food and storage conditions, and appropriate safety and sensory assessment. Only those that retain meaningful efficacy while meeting these requirements should proceed toward food-grade scale-up and regulatory evaluation. The value of sponge-associated actinobacterial metabolites for food biopreservation will ultimately depend on how successfully selected candidates move through these successive biological, technological, and safety requirements, not on antimicrobial potency alone.

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