

A Review on Chemical Profile and Pharmacological Properties of Marine Sponge *Tectitethya Crypta*

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ABSTRACT

Marine sponges have gained recognition as a valuable resource due to their significant pharmacological properties. The investigation of substances produced by sponges has been extensively researched to identify their pharmacological properties. Marine sponges, which are part of the phylum Porifera, are thought to be the main source of marine natural products. Sponges are multicellular organisms that have a number of pores and channels for exchanging water; the secondary metabolites they create are in turn influenced by their specific environmental circumstances. Natural products such as lipids, terpenoids, peptides, alkaloids, and steroids are abundant in the marine sponge genus *Tectitethya crypta*. These compounds have unique chemical structures and have shown promising biological activities, making them ideal candidates for the development of novel drugs to treat various ailments. *Tectitethya crypta* is a sessile filter-feeder that produces a variety of bioactive compounds, including nucleosides and other secondary metabolites. This article reviews the biology and chemistry of *Tectitethya crypta* and serves as an introduction to the organism. We discuss the taxonomic classification, morphology, and microenvironment of the sponge, as well as the chemical structures and biological activities of its bioactive compounds. *Tectitethya crypta* was the source for the development of vidarabine, ara-C, and gemcitabine, which are used to treat viruses and cancer, respectively. We discussed about how these molecules may be used to treat parasitic and infectious disorders.

Keywords: Antiviral drugs, Anticancer drugs, Bioactive compounds, Marine sponges, pharmacological properties.

INTRODUCTION

Marine sponges are the most primitive among multicellular animals that have been included within the phylum Porifera- the "porous animals" of the word. They are mainly open, non-moving animals that adapted to life in the oceans about 600 million years ago by occupying a huge diversity of ecological niches and developing complex interactions with microorganisms¹. By filtering out vast amounts of saltwater, recycling nutrients, and providing various structural shelters to many marine animals, they are important components of benthic ecosystems. The highly efficient filtering mechanism of marine sponges and ability to host an array of microbial symbionts creates complex holobiont, which is probably one of the greatest advantages of their biological success and ecological ubiquity. Marine sponges have attracted much interest in the pharmaceutical industry as abundant sources of naturally occurring bioactive compounds² (Figure 1) Many secondary metabolites from these species possess remarkable pharmacological activities and have diverse structures and physiological activities³.

The distinct chemical entities derived from sponges and their symbiotic microbes have now been recognized as drug development candidates, particularly in areas of investigations such as immunomodulatory, antiviral, anti-inflammatory, anticancer, and antibacterial therapies⁴. One of the remarkable traits of marine sponges is their ability to biosynthesize or accumulate secondary metabolites that apply to ecological process

support such as competition for space, defense against predation, and microbial infection⁵. Such entities frequently have particular scaffolds and configurations of functional groups which are usually not available in terrestrial species-new pharmacological mechanisms for exploitation. The unique structure of these compounds is mostly due to their elaborate biochemical pathways encoded within the sponge and/or its accompanying microbial (bacteria, fungus, archaea, and even microalgae) communities. Marine environments, especially coral reefs and, thus, benthic sites, have an abundance of chemical diversity.⁶ Beyond that the size of the biomass and abundance dominated by the sponges, thereby significantly contribute to the makeup of the benthic population. Defense chemicals have evolved in sponges under the most extreme ecological stresses of the marine environment: limited space, pathogen exposure, and predation. Low doses cause a very strong activity of these agents making them potential leads in the discovery of new drugs having high efficacy with fewer side effects⁷.

Deciphering the sponge species, *Tectitethya crypta* has become one of the most important organisms in the domain of marine pharmacology. The species is originally associated with the Caribbean Sea and has long been known to be important in the marine natural products industry. It is one of the first marine animals from which *spongothymidine* and *spongouridine*, two bioactive nucleoside analogues, were isolated. These nucleosides have generated a new class of effective antiviral and anticancer agents, including the famous cytarabine (Ara-C) and vidarabine (Ara-A)⁸. The chemicals identified from

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Figure 1. *Tectitethya crypta*.

T. crypta transformed the perception of marine organisms as potential sources of drugs and triggered the boom in marine biotechnology research. The pharmacological activities of the bioactive compounds isolated from *T. crypta* are manifold. Cytarabine, for instance, is still in use as the backbone of chemotherapeutic treatment for non-Hodgkin lymphoma and acute myeloid leukemia⁹. There is much therapeutic significance for marine-derived nucleosides since their mechanism involves the interference with DNA systems going into nucleic acid chains. Similarly, before acyclovir was developed, vidarabine became one of the first antiviral medications to see clinical use, particularly against herpes simplex virus infections. The focus here is on the unexplored marine biodiversity as a source for novel medicines and the translational potential of metabolites obtained from marine sponges. Current studies on *T. crypta* and other related organisms have shown the presence of new metabolites with a wide range of bioactivities apart from nucleoside analogue¹⁰.

They include alkaloids, terpenoids, sterols, peptides, and polyketides; many of these show promising preclinical activity. Such molecules are good templates for medicinal chemistry and the manufacture of drugs accompanying their structural complexity and diversity in functions. Moreover, improvements in isolation techniques and high-resolution mass spectrometry-nuclear magnetic resonance (HRMS-NMR) spectroscopy and bioassay-guided fractionation have greatly enhanced our abilities to recognize and describe the novel compounds generated from sponges¹¹. The medicinal importance of *T. crypta* is as a model system for studying symbiotic relations and marine chemical ecology. More and more evidences point to the possibility that many of the bioactive substances extracted from marine sponges are actually derived from the associated microbes rather than from the sponges themselves¹². It has now become possible to identify, clone, and express the biosynthetic gene clusters responsible for their biosynthesis in heterologous systems for large-scale production, and this opens up new avenues in synthetic biology and marine microbial genomics. How these efforts proceed toward resolving the problem of sustainable capture of marine species will contribute to an uninterrupted supply of bioactive materials for drug discovery pipelines in the future^{13,14}. The benefits of the integration of omics technologies, including metagenomics, transcriptomics, and metabolomics, were consistent with increased knowledge regarding the biosynthetic potentials of marine sponges and their respective symbionts. Through these means, scientists might identify new molecular targets for drug development and disentangle convoluted metabolic networks involved in the production of secondary metabolites¹⁵. In tandem with high-throughput screening and SAR studies, these methods further provide a logical pathway for design and optimization of the lead compounds against specific therapeutic indications.

There is an urgent need to develop new therapeutic agents that are more efficacious and safer, considering the vast array of diseases afflicting mankind today, like cancer, viral infections, and resistance to antibiotics^{16,17}. Marine sponges such as *Tectitethya crypta* provide a distinct and little-explored source for such drugs. If their chemical and pharmacological properties are explored further, there is significant scope for the development of next-generation medications. The realization of marine sponge natural compounds' potential must be fulfilled through inter-disciplinary alliances of marine biologists, chemists, pharmacologists and bioinformaticians. This research aims to deep-dive into the pharmacological and chemical profiles of *Tectitethya crypta*. Among the main types of chemicals in this sponge species are their mechanisms and potential applications in medicine¹⁸. Also, the review points out potential approaches to exploit *T. crypta* biomedical potentialities, along with current advances in studying marine natural products. In this way, marine biodiversity will be revealed to the world as an important source of new pharmaceutical innovations and encourage more research into this rich but largely unanalyzed area¹⁹.

TAXONOMICAL CHARACTERS OF TECTITETHYA CRYPTA

Taxonomy Of *Tectitethya Crypta*

Kingdom: Animalia

Phylum: Porifera

Order: Hadromerida

Class: Demospongiae

Family: Tethyidae

Genus: *Tectitethya*

Species: *Tectitethyacrypta*

Morphology

- *T. crypta* has a globular to round or oblong body with the surface either smooth or slightly hispid due to projecting spicules, showing typical characteristics of demosponges.
- Very high tissue regeneration and cellular integrity characterize the sponge, which are adaptations that most marine sponges need for viability in underwater habitat changes.
- Silica spicules in the form of the megasclere(s) (the large spicules) and the microscales (the smaller more fragile spicules) form the interior skeleton and provide structural support^{20,21}.
- The arrangement of these spicules is also important for taxonomy. Depending on its ecology and in relation to its symbiotic bacteria, a sponge can come in a range of colors from light yellow to brown.
- The sponge *T. crypta*, like the rest of the poriferans, does not have true tissues or true organs. Water enters an internal canal system through pores (ostia) that are many in number percolating its body; larger openings known as oscula permit the escape of water²².
- Because of this system of water movement, a sponge can simultaneously discharge waste while filtering out dissolved oxygen and tiny food particles

Habitat And Distribution

Most specimens of *Tectitethya crypta* are found in the Caribbean Sea, which includes areas near the Bahamas, Florida, and other tropical Western Atlantic coastal regions. It usually lives in shallow marine

habitats from one to twenty meters deep. This sponge prefers hard substrates like coral reefs, rocky surfaces, and reef crevices, to which it can attach firmly²³. It is present in coral reef ecosystems and thrives best in warm, well-lighted, and nutrient-rich seas. Dispersal of this species is influenced by environmental factors such as water temperature, salinity, and current flow. It is in the same setting where its filter-feeding lifestyle is supported and symbiotic interactions with other microbial populations are encouraged²⁴.

Ecological Significance

- This *Tectitethya crypta* is probably the ecological services involved in most marine environments by acting as an efficient filter feeder by continuously taking saltwater in, eliminating microorganisms and suspended organic particles through that filtering process.
- Recycling important elements such as carbon, phosphorus, and nitrogen, which are the major contribution to nutrient cycling as it brings the water in, improves its clarity and general quality²⁵.
- Benefit aquatic animal life in the vicinity.
- Numerous tiny invertebrates and microbes can find physical homes and breeding grounds in the sponge. Symbiotic microbial populations are needed for this.
- The compound synthesis which enables it to carry out medicinal activity thrives on such symbiotic relationships²⁶.
- The release of secondary metabolites proves chemical defence systems which not only avoid stinging species from colonizing but also discourage predators²⁷.
- Provide microhabitats to help reduce biofouling on surrounding surfaces and increase biodiversity²⁸.
- The skeletons left behind after death augment the reef structure, aiding towards making it the more stable and physically complex environment.
- Sponges serve a vital role in energy transport by moving energy from the microorganisms and plankton to the upper levels of the trophic cascade²⁹. *T. crypta*, a key bioindicator species, tracks changes in ecosystem health because of its sensitivity to pollution or associated pressure.
- It alters the health dynamics of the reef through competition with algae and corals. Long-term storage of organic carbon contributes to marine systems' carbon storage.
- Distinct compositions of microbial communities also harbor potential biotechnical applications³⁰.
- Lastly, the ecological presence enhances full resilience of reefs, allowing coral reef ecosystems to bounce back and remain self-sustainable.

Chemical Diversity and Structural Features of *T. Crypta*-Derived Compounds

Marine sponges are known for offering an abundance of naturally occurring compounds which differ enormously in their chemistry and physiology³¹. *Tectitethya crypta* is singularly important in terms of marine pharmacology, both scientifically and historically³². The Caribbean sponge has revealed numerous structurally unique secondary metabolites with potent biological activity. Chemicals varying from terpenoids, alkaloids, and nucleosides to other special molecular scaffolds have been isolated from *T. crypta*. Such metabolites can provide a repository of chemical templates for drug development and discovery since they possess structural features that are rare in terrestrial species³³.

Nucleosides: Among the most important contributions of *Tectitethya crypta* to medical chemistry is the identification of the marine-derived nucleosides. In the 1950s, two potent nucleosides with antiviral and anticancer activity were isolated from the sponge: *spongothymidine* and *spongouridine*. These substances are analogs of naturally occurring uridine and thymidine that have been modified to enhance their properties³⁴.

Vidarabine or Ara-A: These compounds are nucleosides that instead of ribose sugar have arabinose sugar. From the time of their discovery, they have turned out to be a valuable source of new compounds, having antiviral and anticancer effects. Vidarabine most likely has derived most of its activity from *spongouridine*, and it is also known as Ara-A³⁵. This synthetic *spongouridine* analogue was found and developed on the structural basis of arabinose sugar and has proven to possess very potent antiviral activity³⁶. In 1960, adenine arabinoside was first discovered by Privat de Garilhe and de Rudder, who reported its antiviral activity, which is the active ingredient of vidarabine. Further studies reported on the efficacy of vidarabine against herpes encephalitis and other rare herpes infections that happen among infants³⁷. Vidarabine, or adenine arabinoside/Ara-A, is a synthetic version of adenosine. It undergoes reaction with 2,3,5-tri-O-Acetyl-D-arabinofuranosyl chloride in the presence of base, normally triethylamine, which brings about the tri-O-acetyl arabinoside derivative of adenine. Then, for the final product, vidarabine, the acetyl groups are removed through basic hydrolysis³⁸. Vidarabine is a compound subjected to extensive modification to improve its therapeutic profile and lessen its toxicity. Derivatives of vidarabine include acyclovir (ACV) which is commonly used as an antiviral drug that is lesser selective and much less toxic compared to vidarabine, and prodrugs of ACV such as valacyclovir (VCV) and famciclovir (FCV). Brivudine (BVDU)-another derivative from vidarabine-used in treating viral infections such as herpes and hepatitis B; ribavirin (RBV)-used in treating respiratory syncytial virus, hepatitis C, and a host of other infections³⁹. These compounds have different chemistries and different mechanisms of action but share nucleoside analog as their common feature. These syntheses involve an alteration of arabinose or adenine moieties with applications of halogens or other functional groups to magnify potency or selectivity as part of the chemical synthesis of these derivatives. Syntheses of these compounds usually require a multi-step reaction course in a specialized setting with a high degree of expertise⁴⁰.

Spongothymidine: *Spongothymidine* is a nucleoside that was first discovered back in 1950, from a Caribbean sponge species, *Tethya crypta*. Various studies conducted over time have shown the possible medicinal properties of this compound, most importantly, as an antiviral and anticancer agent. *Spongothymidine* was found to have strong antiviral activity against a wide structural range of viruses including herpes simplex virus, varicella zoster virus, and vaccinia virus. It inhibits viral replication and the antiviral activity has been attributed to interfering with the synthesis of viral DNA. The compound is the basis for the development of synthetic antiviral drugs, the most prominent being vidarabine. Besides its antiviral properties, *spongothymidine* also exhibits promising anticancer activity. It has been shown to hinder growth in cancer cells of several types including breast, colon, and lung carcinomas. *Spongothymidine* is that inhibits the action of thymidine kinase. It is one of those enzymes that are responsible for the DNA replication process within the cancer cells in the body; hence, it inhibits cell proliferation and leads to ultimate apoptosis. Further evaluation has been done to consider *spongothymidine* as a candidate for an antiparasitic agent. The compound displayed significant activity against *Leishmania major*, the causative agent of cutaneous leishmaniasis, a disease affecting millions of persons across the globe⁴¹. It has also been studied for its potential action against HIV and Ebola. HIV replication was shown to be inhibited in vitro; some investigators suspect that

spongothymidine may be useful in developing new treatments for this disease. *Spongothymidine* was shown to have activity against Ebola in vitro, thus some studies have suggested it might be a potential treatment for Ebola. On the whole, the medicinal properties of *spongothymidine* make it a compound of great interest for developing new antiviral and anticancer therapies. Further studies have yet to confirm its potential uses and design safe and effective drugs from them. The drug *spongothymidine* and its derivatives are being synthesized chemically for these medicinal applications. One synthetic pathway is through the formation of arabinosylthymine derivatives, closely resembling their structure to that of *spongothymidine*⁴². For example, synthesis of 1-(2'-deoxy-2'-fluoro-1-beta-D-arabinofuranosyl)-5-methyluracil (FMAU) was achieved and the compound tested for antiviral and antitumor properties, indicating some promising responses in preclinical studies. Other derivatives of *spongothymidine* have been synthesized; for example, 3'-deoxy-3'-fluoroarabinosylthymine (3'-F-ara-T) and 3'-deoxy-3'-chloroarabinosylthymine (3'-C-ara-T). These compounds showed antitumor activity, while 3'-F-ara-T is currently undergoing clinical trials in the treatment of leukemia and lymphoma. In addition to those already mentioned, the synthesis of *spongothymidine* and its derivatives⁴³.

Spongonucleosides: Spongonucleosides compose an extraordinary class of natural nucleoside analogues, first obtained from marine sponges, namely *Tectitethya crypta*. These substances attracted attention due to their structural similarity to naturally occurring nucleosides, the building blocks of nucleic acids; however, slight structural variations engender great biological activity and, thus, require them to be deemed essential building blocks in the design of antiviral and anticancer drugs⁴⁴. As in classical nucleosides, these spongonucleosides are comprised of a nitrogenous base (being either purine or pyrimidine) attached to a sugar moiety via a β -glycosidic bond. Contrary to their terrestrial cousins, which exhibit usual structural characteristics, spongonucleosides often possess unusual alterations that accentuate their bioactivity. For instance, spongosine, one of the first identified spongonucleosides, had a core of 9- β -D-ribofuranosyl-2-methyladenine. A methoxy group substitution at the purine ring's 2-position gives this molecule some variation from adenosine⁴⁵. This substitution not only alters the compound's hydrogen bonding properties but also further increases its resistance to enzymatic degradation, thus improving its pharmacokinetics. 2'-deoxy- sponge- sultam, similarly to deoxyribonucleotides in DNA, is yet another important compound and does not have a hydroxyl group at position 2' of the ribose ring. Its absence is paramount because once introduced into the opposite strand of a replicating DNA, it would terminate DNA synthesis and exert possibly cytostatic or cytotoxic effects. Ara-t (arabinosylthymine), where the sugar moiety is arabinose instead of ribose, is another significant analogue. This stereochemical difference will affect the absorption of the molecule into nucleic acids while inhibiting DNA polymerases—a mechanism targeted in antiviral therapy. Other oxidatively modified nucleosides are spongonucleosides such as 8-oxo-2'-deoxyguanosine⁴⁶. Guanine is an important marker of oxidative stress because of the presence of an oxo group at position 8; however, it also serves to alter DNA repair pathways and base-pairing fidelity. Structural features of these compounds include planar hydrogen-bonding purine or pyrimidine bases stacked against the conformationally flexible sugar moieties. The variety of sugars (ribose, deoxyribose, and arabinose) and base modifications (oxidation and methylation) endowed these compounds with multiple biochemical behaviors⁴⁷.

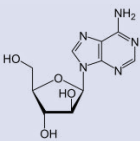
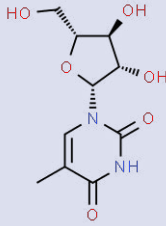
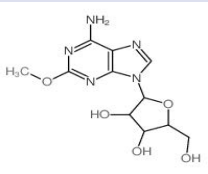
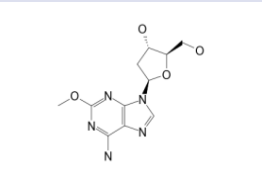
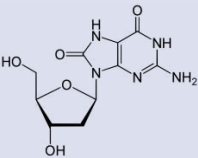
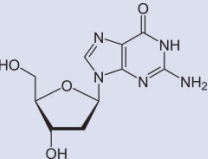
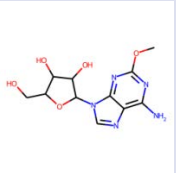
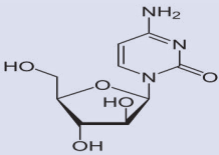
Cytarabine: Arabinosyl nucleosides are interesting examples of this chemical family: *spongothymidin* and *spongouridine*, which were isolated from the marine sponge *Tectitethya crypta* and served as the cradle for the development of cytarabine (Ara-C), which is a synthetic

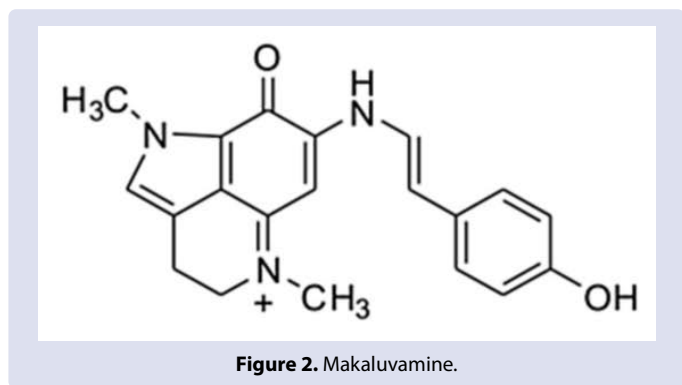
chemotherapeutic agent⁴⁸. The invention pertaining to cytarabine arose when the sugar considered to be at the very basis of these extraordinary molecules was arabinose as opposed to ribose, known in other nucleosides and nucleoside analogues. *Spongothymidine* and *spongouridine* were isolated from *T. crypta* in the early 1950s and presented with distinct sugar moieties, namely arabinose instead of the common ribose found in human nucleosides. These arabinosyl nucleosides provided the structural basis of synthetic analogues and well-defined biological activities. Cytarabine is a chemical analogue of a pyrimidine nucleoside⁴⁹. It can be classified as cytosine arabinoside, the nucleobase cytosine joined to arabinofuranose. The stereochemistry of the sugar moiety makes it distinctive. In contrast with ribose, the arabinose sugar's 2'-hydroxyl group in cytarabine is orientated opposite. This small yet significant alteration in structure makes DNA polymerase not able to elongate as it should during replication. The sugar-base bond of cytarabine, a β -N-glycosidic bond, attaches the N1 position of the cytosine ring to the 1' carbon of arabinose⁵⁰. Cytosine's planar configuration allows normal base pairing with guanine, but this modified sugar backbone gives rise to steric hindrance when incorporated into DNA strands. Cytarabine's genesis stems from using arabinosyl nucleosides isolated from *T. crypta*, which in turn serve as templates for laboratory-scale synthesis⁵¹. This truly marked a watershed moment in marine natural product chemistry that saw new drug leads being discovered from various marine sources. Cytarabine's unique structure designates it as an antimetabolite in therapy, thus inhibiting DNA synthesis in fast-proliferating cells, especially those associated with leukaemias. (Table 1) Cytarabine's heredity from *Tectitethya crypta* strongly hints at the importance of marine resources in current medicinal chemistry and drug development⁵².

Alkaloids: The nitrogen secondary metabolites or alkaloids possess well-known effects such as antibacterial, antifungal, antiviral, anticancer, and anti-inflammatory effects. Marine sponge alkaloids have established unusual structural features that usually are not found among terrestrial alkaloids, like sophisticated ring systems and halogenated substitutions⁵⁶. The *T. crypta* alkaloid is not studied to the maximum extent, as the nucleosides have garnered more attention, but reports in other closely related Tethyidae sponges have yielded nitrogenous compounds of considerable value. Thus, it can be assumed that *T. crypta* also produces some alkaloids structurally similar to those or probably supports microbial communities capable of synthesizing them based on their taxonomic and ecological affinities⁵⁷. Pyrroloiminoquinones, indole alkaloids, and quinoline-type alkaloids are types of alkaloids commonly encountered in demosponges and possibly in *T. crypta*. The intense cytotoxicity or antibacterial properties of these compounds are largely attributed to their planar aromatic structures allowing the intercalation of DNA or inhibition of enzymes. These alkaloids could serve as chemical defenses in marine ecosystems against microbial attack, predators, or competition with other sessile organisms. Alkaloids therefore represent versatile pharmacophores due to the presence of basic nitrogen atoms, which enable interactions with diverse biological targets via ionic and hydrogen-bonding interactions⁵⁸. Environmental factors such as temperature, salinity, and nutrient availability can affect the production of these alkaloids and are often mediated by the action of microbial symbionts within the sponge⁵⁹. Until now, metagenomic and microbiological studies have thrown light on the presence of biosynthetic gene clusters for alkaloid biosynthesis, though there is scant literature to this effect of direct isolation of certain alkaloids from *T. crypta*. Such developments may possibly act as encouraging lead-in guides for further studies towards revealing the discovery of new alkaloid scaffolds with possible medicinal applications⁶⁰ (Figure 2).

Terpenoids: Another very important group of secondary metabolites found in the marine sponges *Tectitethya crypta*, is terpenoids,

Table 1. Major compounds isolated from *Tectitethya crypta*^{53,54,55}.

Fig. No	Name of the compound	Structure
	Vidarabine or Ara-A	
	Spongothymidine or Ara-T	
	Spongosine	
	2'-deoxyspongosine	
	8-oxo-2'-deoxyguanosine	
	2'-deoxyguanosine	
	2-methoxyadenine	
	Cytarabine	



commonly known as isoprenoids. These compounds, ranging from simple monoterpenes to more complex sesterterpenes and triterpenes, are biosynthesized from five-carbon isoprene units. Apart from those rare skeletal structures, different from most terres-trial species, marine terpenoids are also those frequently containing high oxygen as well as halogen. There is a strong assumption that *T. crypta* might contain these terpenoids since certain terpenoids already exist in similar sponge species, although specific terpenoids for this organism are not very well characterized yet⁶¹. Terpenoids from *Tethya* species have been further documented for their therapeutic potential because they have evidence of cytotoxicity, antifungal, antiprotozoal, and anti-inflammatory activities. The mesohyl matrix of marine sponges can be home to symbiotic microorganisms, including archaea and bacteria that might, in turn, be responsible for the biosynthesis of terpenoids, directly or indirectly. The microorganisms in question contain terpene synthase genes that enable them to synthesize highly complex terpenoid compounds, which are often characterized by an explicit stereochemical specification⁶². The symbiotic biosynthetic origin of these substances has been confirmed often due to gene expression analysis, metagenomics, and microbial culturing. Marine terpenoids also exhibit structural features associated with their uniqueness and reactivity toward biological macromolecules including epoxide rings, lactone functions, peroxide bridges, and polycyclic scaffolds. These very same structural features not only enhance their biological activity but also make them attractive targets for synthetic modification in drug development. Certain sponge-sourced terpenoids have entered preclinical and clinical phases since they are potent against cancer cell lines and a variety of pathogens. It is highly plausible that similar discoveries will be made with *T. crypta* in the near future, given the novel advances in chemical isolation, spectroscopy, and genomic tools⁶³.

PHARMACOLOGICAL ACTIONS AND POTENTIAL THERAPEUTIC APPLICATIONS

Antiviral Activity

Antiviral activity of *Tectitethya crypta* is one of its most established pharmacological characteristics because of nucleoside derivatives, *spongouridine*, and *spongothymidine*. These nucleosides containing arabinose played an important role in the first production of antiviral medicines from marine sources. Ara-A, a synthetic version of *spongouridine*, became one of the earliest-ever approved antiviral drugs for humans⁶⁴. Because it substituted arabinose for ribose, this drug mimicked adenosine and entered into virus DNA during replication, causing chain termination and halting synthesis of the DNA entirely and thus preventing spread of the virus. Vidarabine has been effective against varicella-zoster virus and also very significantly active against herpes simplex virus types 1 and 2, more so in immunocompromised individuals and babies suffering from herpes encephalitis. The improved pharmacokinetics and decreased toxicity

of the newer nucleoside analogues like acyclovir and valacyclovir were, in fact, developed in light of the success of Vidarabine⁶⁵. Although synthetic in nature, the basic tenets for the design of these medicines were derived from the natural metabolites of *T. crypta*. Another major aspect of antiviral drug development is the mechanism of action of vidarabine: the selective inhibition of viral DNA polymerase with no effect on host cell replication. Current work seeks to discover new compounds from *T. crypta* and its symbionts against resistant viral strains like HIV, HCV, and emerging zoonotic viruses. Bioinformatics and metagenomic analyses of sponge microbiota have revealed putative genes for antiviral polyketides and non-ribosomal peptides, which hint towards the untapped potential of *T. crypta* in the realm of chemical investigation⁶⁶. Later studies indicated that acyclovir (Zovirax) was, in fact, the drug of choice for herpes virus infections. Vidarabine inhibits the synthesis of viral DNA. In vivo kinases produced by the virus convert viral DNA into adenine arabinoside triphosphate (ara-ATP), thereby inhibiting viral DNA polymerase and preventing varicella, herpes, and vaccinia viruses from synthesizing their own DNA. Another study provides evidence for a different mechanism of action of the drug, suggesting that vidarabine is actually incorporated into RNA and DNA. Within this context, chromatin-bound poly (A) polymerase would be rendered incompetent to fully catalyze the very first polyadenylation reaction of RNA in the presence of vidarabine. (Figure 3) It has been recently confirmed that vidarabine is 3-5 times more effective than cidofovir (Vistide) in the reduction of viral plaques in vaccinia and cowpox viruses^{67,68}.

Anticancer Activity

The sea sponge *Tectitethya crypta* is one of the critical sources of bioactive compounds with important anticancer effects. The discovery of arabinose-containing nucleosides *spongouridine* and *spongothymidine* which lend themselves as the molecular basis of numerous significant anticancer agents, has indeed transformed the paradigm of the natural products study. In contrast to traditional nucleosides, these attributes are arabinose instead of ribose, which dramatically modify the mode of action with biological enzymes and nucleic acids. Among the most anti-cancer agents is cytarabine (Ara-C), a synthetic analogue of *spongothymidine* inspired by *T. crypta*⁶⁹.

The anticancer properties of cytarabine, best known as an injectable drug, have played a crucial role in most chemotherapy regimens notably in diseases involving the bone marrow such as non-Hodgkin's lymphoma, acute myeloid leukemia (AML), and acute lymphocytic leukemia (ALL). By integrating DNA into the S-phase of the cell cycle, in which DNA synthesis is sterically hindered by the arabinose moiety so as to terminate DNA synthesis prematurely, rapidly replicating cancer cells undergo apoptosis. Cytarabine is effective due to its preferential entry into tumor cells and inhibition of DNA polymerase, which is crucial for DNA replication⁷⁰. After entering the cells, cytarabine gets phosphorylated to Ara-CTP, an active triphosphate form that competes with deoxycytidine triphosphate for inclusion in DNA. The result is damaged DNA, which in turn activates repair



mechanisms within the cell that lead, eventually, to cell death. Due to the efficiency of execution, numerous derivatives of cytarabine have been synthesized to exhibit improved pharmacokinetic properties and reduced toxicity. Such as gemcitabine which is generally used in solid tumors like that of pancreatic, breast, and non-small-cell lung cancers. Besides nucleoside analogues, the preliminary study findings have also revealed the possible presence of various groups of compounds having cytotoxicity against cancer cells—for instance, terpenoids, alkaloids, and fatty acid derivatives in *T. crypta*. They are assumed to affect signaling pathways that control cell proliferation, angiogenesis, and metastasis. Although these non-nucleoside components still need exploration, early bioassay-guided extraction-cum-cell line screenings have shown potential cytotoxic activity enough to propel further investigations. In addition, there are the symbiotic microorganisms which also contribute to the anticancer potential of *T. crypta*⁷¹. Numerous marine sponge-associated bacteria and fungi possess biosynthetic gene clusters coding for non-ribosomal peptides, polyketides, and other secondary metabolites having known properties with antitumor activity. These biosynthetic pathways are currently being discovered under metagenomic and metabolomic approaches. *Tectitethya crypta* has played a crucial role in the discovery and development of anticancer drugs. First, it gave its name to the first really chemotherapeutic drugs coming from marine sources, and today it is the source of natural metabolites which inspire even new drugs. This organism will become fundamental for research in marine pharmacy on the premise of producing more structurally diverse and mechanistically novel anticancer drugs as advanced analytical and genomic methods progress⁷². (Figure 4).

Antibacterial Activity

The potential antibacterial activity of marine sponge *Tectitethya crypta* is what has prompted increased interest in marine organisms as new sources of antimicrobial agents. Marine sponges have evolved bioactive compounds of amazing potency, as continuously being exposed to an extremely rich and variable microbial environment usually necessitates such a condition to fight down bacteria colonization. Particularly metabolite candidates, which are often unique in structures and processes, are attractive approaches to antibiotic development, owing to the emergence of antibiotic resistance⁷³. *T. crypta* extracts also possess antibacterial potentials that research have recently demonstrated, in addition to the nucleoside analogues identified, such as spongouridine and spongothymidine. Crude and somewhat purified extracts of *T. crypta* display moderate to strong inhibitory activity against various pathogenic bacteria including *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*. Such activities suggest the presence of numerous bioactive compounds, including peptides, fatty acids, terpenoids, and alkaloids⁷⁴. They are thought to exert action against bacteria by disrupting membranes, inhibiting the synthesis of proteins, interfering with nucleic acid replication, and inhibiting cell wall formation. Unlike most traditional antibiotics, some marine-derived compounds have their own special combination of architectural motifs, such as Sulphur bridges, brominated rings, or odd sugar moieties, which may allow them to evade the usual mechanisms of resistance. One of the most interesting aspects is the role of the microbial symbionts associated with *T. crypta* in providing such antibacterial activity⁷⁵. Many secondary metabolites with antibiotic activity can be produced

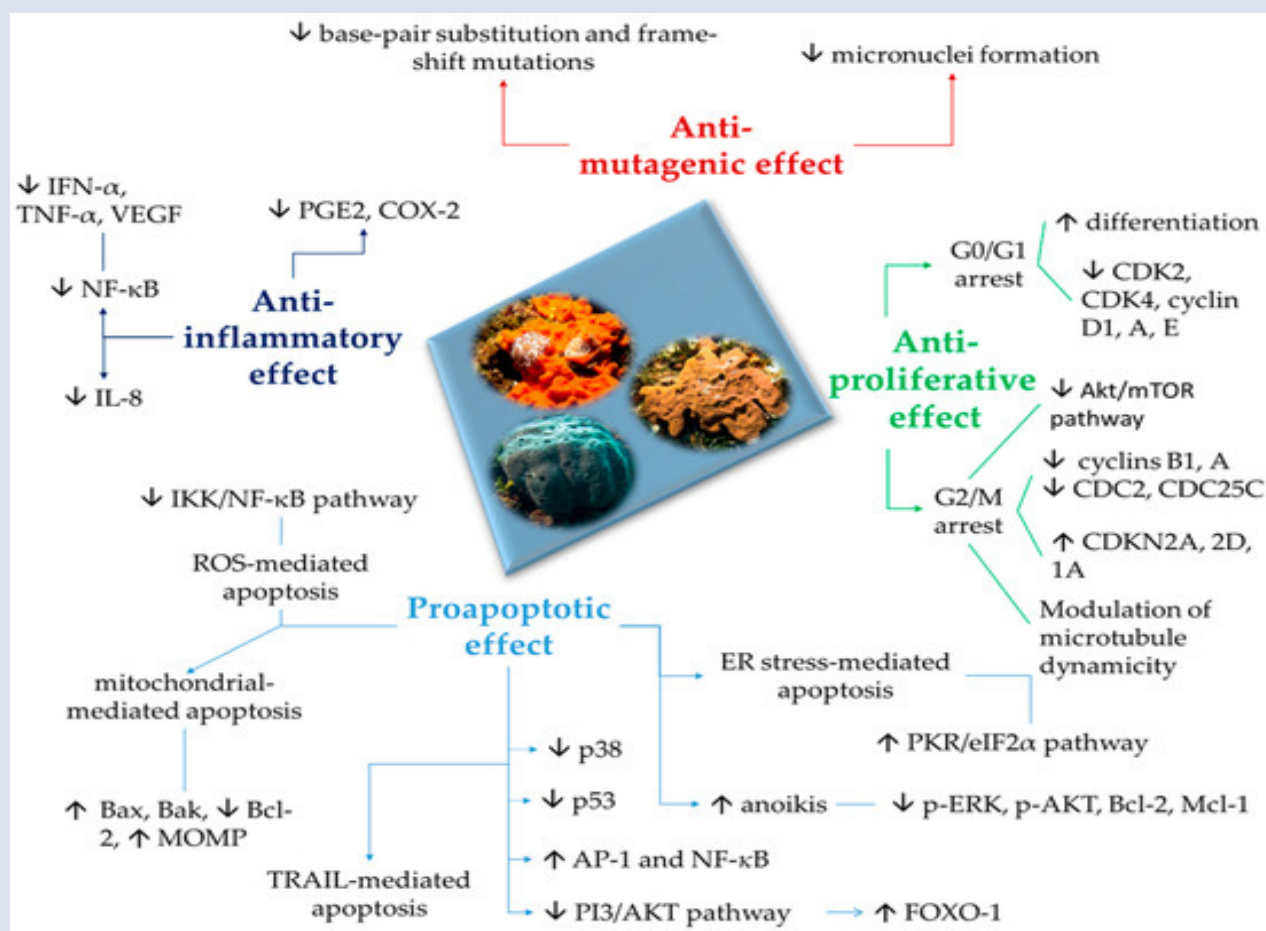


Figure 4. Pathways by which the marine chemicals' anti-mutagenic, anti-inflammatory, anti-proliferative, and proapoptotic actions occur.

by a number of bacterial communities living in marine sponges. In such conditions, the microbial associates may be responsible for the production of polyketides and nonribosomal peptides (NRPs) that are believed to possess strong antibacterial activity. Metagenomic studies of the *T. crypta* microbiome highlight the identification of biosynthetic gene clusters associated with these pathways, reinforcing its role as a potential source of novel antibiotics⁷⁶. The compounds isolated from *T. crypta* are therefore of great interest in antibiotic development, especially in the face of increasing multidrug-resistant bacterial infections. Further studies targeting bioassay-guided isolation, elucidation of structure, and mode of action investigations could warrant the discovery of better antibacterial drugs. Besides therapeutic potentials in viral infections and cancer, *Tectitethya crypta* has a lot of other prospects⁷⁷.

Antifungal Activity

Tectitethya crypta is a benthic organism that has always lived closely with a diversity of marine microbes, has developed complex methods for chemical defence in its microbe-rich and highly competitive habitats. One means of defense is the production of secondary metabolites, which inhibit fungal and pathogenic strains. Although it's well known for its nucleoside analogues such as *spongouridine* and *spongothymidine*-structures that have been bases for antiviral and anticancer medicines-increasingly recognized evidence now shows that extracts from this sponge also have antifungal activity⁷⁸. Preliminary tests using methanolic and ethyl acetate extracts of *T. crypta*, in crude and semi-purified forms, have displayed inhibitory activity against a variety of fungi such as *Aspergillus Niger*, *Candida albicans*, and *Cryptococcus neoformans*. Bioactive compounds, the active agents are believed to be terpenoids, alkaloids, and fatty acid derivatives that perform antifungal activities in *T. crypta*. Their mode of action could involve intervene in fungal DNA and protein synthesis or disrupting the fungal cell membrane or inhibition of ergosterol, a sterol that is a major component of fungal membranes⁷⁹. Certain terpenoids derived from the sponges have been reported to induce ion disequilibrium within fungal cells, leading to cell death through the formation of pores on the fungal membrane. Also, the microbial symbionts associated with *T. crypta* may be another potential source of antifungal chemicals, as they could produce particular antimicrobial metabolites absent in terrestrial species. In research, it was recently observed that there were biosynthetic gene clusters in bacteria associated with sponges known to produce strong antifungal polyketide and non-ribosomal peptide compounds⁸⁰. This implies that some of the antifungal compounds credited to *T. crypta* might originate from its associated microbiota. These compounds are not only antifungal but also possess special structural features that give rise to novel scaffolds for synthetic alteration. Given the increase in resistance to conventional antifungal agents such as azoles and echinocandins, this becomes very encouraging. Therefore, discovery and development of antifungal compounds from *T. crypta* would possibly lead to a new way for therapy.

Anti-inflammatory Activity

The marine sponge *Tectitethya crypta* has attracted scientific interest owing to its various pharmacological properties. Among these, the anti-inflammatory properties stand out as a promising treatment option. Inflammation is the body's natural immune response to injury or infection, but disordered inflammation leads to chronic conditions such as arthritis, heart failure, and neurological diseases. Studies on natural substances that prevent inflammation have increased, and marine sponges—especially *T. crypta*—appear to be viable candidates in the search for effective anti-inflammatory agents⁸¹. The anti-inflammatory properties of *T. crypta* are mainly attributed to the presence of different classes of secondary metabolites such as nucleoside analogues, alkaloids, and terpenoids. They have been found to interfere with the inflammatory signaling pathways that are crucial such as the nuclear factor-kappa B (NF- κ B) pathway, which is required for the production of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6. Blocking activation of NF- κ B, whereby production of these mediator events becomes transcriptional, leads to a decrease in levels of inflammation. *T. crypta* extracts, especially methanolic and ethyl acetate fractions, have proven effective against several inflammatory markers both in vitro and in vivo. Sponge-derived compounds were shown to inhibit the enzymes cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) by decreasing the amount of prostaglandin E2 (PGE2) and nitric oxide (NO) released in lipopolysaccharide (LPS)-stimulated macrophage cell culture studies. These drugs are in fact known as anti-inflammatory agents which inhibit the above-mentioned enzymes⁸². "A unique feature of such metabolites generated from *T. crypta*, like halogenated sugar moieties and arabinose-linked nucleosides, is that it can effectuate specific binding to inflammatory mediators. Such affinity may offer less adverse effects than those caused by synthetic anti-inflammatory compounds. Apart from inhibiting pro-inflammatory pathways directly, *T. crypta* chemicals may be immunomodulatory by changing the polarization of macrophages and reinforcing anti-inflammatory M2 skewed phenotypes. Certainly, that type of modulation is useful when considering chronic inflammatory diseases, as here the main contributing factor is immunological dysregulation (Table 2).

Advances In Analytical Techniques for Compound Isolation and Characterization

Marine natural products are complex and diverse, and this complexity demands that modern analytical techniques be combined with isolation and characterization of bioactive compounds from marine plants like *Tectitethya crypta*. These analyses require high sensitivity, precision, and complementarity since bioactive compounds often exist in minute quantities in mixtures of heterogeneously structured substances. The foremost approaches employed in marine natural product exploration include NMR spectroscopy, HRMS, chromatographic methods in combination with bioassay-guided fractionation.

Table 2. Derivatives from *Tectitethya Crypta* and its Extraction, Activity, Application, and marketed state⁸³.

PHYTOCONSTITUENTS	EXTRACTION METHOD	ACTIVITY	APPLICATION	MARKETED/UNMARKETED FORM
<i>Spongouridine</i>	Methanol extraction	Antiviral	Viral infections	Not marketed yet
Cytarabine (Ara-C)	Synthetic derivative	Anticancer	Leukemia, lymphoma	Cytosar-U
Vidarabine (Ara-A)	Synthetic derivative	Antiviral	Herpes	Vira-A
Gemcitabine	Synthetic analog	Anticancer	Pancreatic, breast cancer	Gemzar
Brivudine	Synthetic analog	Antiviral	Herpes zoster	Zostex
Ribavirin	Synthetic analog	Antiviral	Hepatitis C, RSV	Copegus, Rebetol
Acyclovir	Synthetic analog	Antiviral	Herpes simplex, varicella	Zovirax
Valacyclovir	Prodrug of acyclovir	Antiviral	Herpes simplex, varicella	Valtrex
Ara-G (Nelarabine precursor)	Synthetic derivative	Anticancer	T-cell leukemia	Arranon
Fatty acid derivatives	Lipid extraction	Antibacterial	Infectious diseases	Experimental

Nuclear magnetic resonance (NMR)

This spectroscopy is counted among the most promising techniques for structure elucidation. It provides information about the molecular structure, stereochemistry, functional groups, and connectivity of carbon and hydrogen. 1D and 2D NMR methods including ^1H NMR, ^{13}C NMR, COSY, HSQC, HMBC, and NOESY have been employed most often in combing the entire structure of isolated marine sponge molecules. Contemporary NMR instruments, particularly those operating at 600 MHz or above, provide sensitivity and resolution that can work with very small volumes of material which is very important in isolating compounds from rare sponges like *T. crypta*. Such information was included in the training for the models as data till October 2023.

High-Resolution Mass Spectrometry (HRMS)

These techniques boost NMR with Mass High-Resolution Spectrometry, which supplies precise information on weight and elemental makeup of molecules. Besides, these methods have been employed in marine pharmacology for putting up the verification of molecular formulae, whereby some of these methods include the contribution of electrospray ionization (ESI), matrix-assisted laser desorption/ionization (MALDI), and time-of-flight (TOF) analysers. When differentiating the isotopic patterns, this comes very well handy to identify halogenated or highly transformed nucleoside analogues of *T. crypta* since the presence of elements like bromine and chlorine can be differentiated using isotopic patterns. It is the dereplication where HRMS is involved, which is recognizing the known compound relatively early in the screening process against redundancy and detecting small components in complicated extracts.

Chromatographic techniques

The aforementioned techniques of chromatography prove to be very useful when the separation purification of chemicals is marine-source, especially high-performance liquid chromatography (HPLC) or gas chromatography (GC). Effective separation of structurally identical molecules, including stereoisomers, can therefore be achieved by HPLC, particularly in combination with mass spectrometry (LC-MS) or diode-array detection (DAD). Reverse-phase HPLC is the most often employed separation technique for marine extracts, since a majority of the metabolites produced by sponges tend to be polar. With preparative-scale HPLC, a researcher can isolate milligram quantities of pure chemical compounds for subsequent structural and biological analysis. While GC can be used to profile fatty acids and volatile compounds, it has been rarely applied to metabolites from marine sponges.

Bioassay-guided fractionation

This is a process of carrying out biological tests associated with chemical fractionation to purify the active compounds from the extracts. Such extraction-fractionation-biological activity testing is repeated for sponge material until the active principle is isolated from the obtained fractions. Keeping aside the promising activity-producing fractions, further sub-fractionation and analyses occur⁸⁴. The approach is significant, even today, for the identification of important pharmacological compounds such as *spongouridine* and *spongothymidine* Culled from *T. crypta* from where they later inspired the synthesis of vidarabine and cytarabine. The combination of these analytical techniques results in a synchronous and efficient method in the identification of new natural products. NMR gives an overall structural picture, whereas HRMS gives the precise molecular weights; chromatography separates effectively, while bioassay-guided fractionation links the chemical ID with function.

Challenges and Future Prospects in Marine Drug Discovery

Marine ecosystems, especially sponges such as *Tectitethya crypta*, represent a fascinatingly rich but largely undiscovered reservoir of bioactive compounds of immense pharmacological potential. In the last few decades, diversity from the marine environment has been the source of some very interesting leads for drug development with antiviral, anticancer, antibacterial, antifungal, or anti-inflammatory activity in different parts of the world. However, numerous other hurdles come in the way of rendering these natural marine products into drugs approved for clinical use, including sustainability-related issues, challenges with large-scale production, limited availability at times of relevant compounds, and technical challenges. However, with the advent of synthetic biology, genomics, and bioengineering, some modern solutions lie on the horizon and stir some optimism for marine pharmacology⁸⁵.

The sustainability of harvest and utilization represents a serious concern to bioactive substance production. Marine organisms, such as sponges, produce bioactive compounds that are often available in trace quantities. The excessive harvesting of marine sponges from the ocean to ensure sufficient material for study or commercial use may lead to ecological disturbance and habitat destruction. Sufficient harvesting of substantial amounts of tunicate crypta, like many marine sponges, would not be biologically feasible as it is critical to the benthic ecosystem dynamics. Investigations are thus being carried out in sustainable collection strategies, the likes of aquaculture and mariculture. These include the raising of marine life in controlled environments against the demand, posing no risk to wild populations. Yet another major issue has arisen in the manufacture of bioactive substances on a commercial scale. The labyrinthine chemical properties of many marine natural products create obstacles for their synthetic attempts in the laboratory, thus rendering it uneconomical. Commercial manufacturing is inefficient because traditional chemical synthesis frequently entails drawn-out, multi-step procedures with low yields. This issue is made worse when a compound's action is connected to particular stereochemistry or distinctive halogenation patterns, as is the case with many nucleosides and alkaloids originating from sponges. Metabolic engineering and synthetic biology have become viable approaches to addressing production problems. The biosynthetic gene clusters (BGCs) that produce these chemicals in sponges or their symbiotic microbes are now being identified and cloned by scientists.

After being identified, these gene clusters may be introduced into host organisms that are easily cultivated, such *Streptomyces* species or *Escherichia coli*, enabling heterologous expression and scale manufacture of the targeted chemicals. By providing sustainable supply options, this strategy also presents opportunities for the development of analogues with better medicinal properties. The future development of marine pharmacology seems to rely heavily on the synergistic application of modern omics technologies, such as proteomics, metabolomics, transcriptomics, and genomes. These technologies allow for the rapid identification of bioactive compounds and their biosynthesis pathways from rare or uncultivated marine species. Meanwhile, drug discovery systems powered by artificial intelligence are under development, functioning in accelerating lead optimization and predicting the bioactivity of novel marine compounds. In addition, in silico modeling and high-throughput screening (HTS) are speeding up the early phases of drug development by facilitating the fast identification by scientists of the therapeutic potential of large chemical libraries. A more directed and efficient discovery pipeline will be afforded by the use of these technologies along with bioassay-guided fractionation. Economic and regulatory factors strongly influence marine drug development in the future. In this regard, it is imperative

to protect the rights of intellectual property, navigate rules of access to marine biodiversity (such as the Nagoya Protocol), and ensure fair practices in bioprospecting to encourage international partnership and investments in marine biotechnology. New technological advances, therefore, promise intriguing solutions to problems that still resist the development of drugs from marine sources, including sustainability, complex synthesis, and limited natural availability. AI, omics technologies, and synthetic biology are enabling us to study marine pharmacology more efficiently, ethically, and sustainably. Marine sponges such as *Tectitethya crypta* seem poised to contribute to the next generation of drugs capable of fulfilling unmet medical needs in the treatment of numerous disorders, provided that multidisciplinary collaboration and innovation will continue.

CONCLUSION

As one of the distinguished marine pharmacological sponges associated with the discovery of a large number of bioactive compounds with potential medicinal uses, a *Tectitethya crypta* has been found to be a rich source of structurally distinct and diverse metabolites, including terpenoids, alkaloids, and nucleosides, which have propelled innovations to significant pharmaceuticals over time. Some of the examples of such metabolites are *spongouridine* and *spongothymidine*, which led to many early antiviral and anticancer agents such as vidarabine and cytarabine, respectively. This discovery has shaken up the entire industry and held up vast unexplored chemical diversity that exists in the marine world. It has a large spectrum of pharmacological activity such as antiviral, anticancer, antibacterial, antifungal, and anti-inflammatory compounds derived from *T. crypta*. These metabolites can be very good leads in drug development because they can interact with a variety of biological pathways including immuno-regulatory mechanisms, inhibition of enzymes, and synthesis of DNA and RNA. Their mechanisms of action and the likelihood of structural modification gave rise to drug compounds that have been even more potent, selective, and safer. Yet, *T. crypta* possesses several challenges towards realizing its full potential. The high-scale application has been complicated by sustainability challenges, its limited naturally available quantity, and the complications linked to separating its compounds. However, in recent years, the identification and structural elucidation of marine natural products has greatly improved due to advances within analytical methods including NMR, HRMS, chromatography, and bioassay-guided fractionation. Moreover, through the introduction of bioactive compounds into the culture medium using heterologous hosts, metabolic engineering and synthetic biology provide an important vehicle for addressing supply concerns. The sustainable harvesting of marine organisms, ethical approaches to bioprospecting, and environmental protection should be integrated early in the marine drug discovery process. The accelerated identification and development of new marine-derived pharmaceuticals will be based on omics technologies, machine learning, and high-throughput screening. Evidence of how marine drug discovery affects modern medicine constitutes the justification for the investigation of marine biodiversity toward drug discovery. With a 360-degree view, research, innovation, and sustainable resource management will give further impetus to the realization of therapeutic potentials from *T. crypta* and related marine species for the treatment of complex and newly emerging diseases.

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