LITHISTID SPONGES DERIVED COMPOUNDS AND THEIR IMPORTANCE IN BIOLOGICAL RESEARCH - A REVIEW

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ABSTRACT
Lithistid sponges have an important source of complex natural compounds with biological activities. The lithistid sponges are of interest to biomedical science because of the great variety of pharmaceutically relevant biological activities of their chemical extracts and are considered as economically important. The compounds identified in these sponges have therapeutic potential and have been frequently hypothesized to contain compounds of bacterial origin. The peptides identified from these lithistid sponges are found to be the sources of antifungal activity. The active agents of these sponges also have cytotoxic and immunosuppressive activities. Many of the cyclic peptides of lithistid represent the anti-HIV activity. The different structure and biological activities of the compounds derived from these sponges have more chemical aspects too.

Keywords: Lithistid sponges, Biological compounds, Anti-fungal activity, Anti-HIV activity.

Introduction
Lithistid demosponges are progressively growing population of marine sponges and are of particular interest to paleontology [1,46]. A few species of lithistid has physiological and ecological traits and biotechnological and ecological uses[23]. These are the largest group of demosponges with polyphyletic nature and are associated with microorganisms [45,48]. They have the capacity to withstand any climatic and chemical conditions [3,4]. The lithistid sponges are of interest to biomedical science because of the great variety of pharmaceutically relevant biological activities of their chemical extracts and are considered as economically important. Early works had laid the findings of many compounds synthesis by microorganisms that line in association with these lithistid and are natural that are non-toxic than the synthetic compounds [10]. Lithistid produces bio-active metabolites and exotic marine natural products. There are metabolites of an invertebrate which are also present in this sponge and it can able to produce secondary metabolites also [44]. The compounds derived are used in cytotoxic and proliferation assays. Separation of the bioactive compounds is based on the biochemical techniques. Early investigations gave rise to broad surveys of these lithistid sponges for natural products with useful biological properties.

Natural products are often structurally complex compounds that possess a well-defined spatial orientation. Those chemical compounds evolved to interact efficiently with their biological targets; therefore, they occupy a biologically relevant chemical space and represent validated starting points for drug discovery [24,23]. Almost all of the current natural product-derived therapeutics has terrestrial origins. However, mining novel sources, such as the marine environment, will clear the way for chemical and biological novelties as well [4,9,11].

The path for drug discovery from natural sources faces several challenges, starting with the access to the marine environment followed by chemical and biological characterizations of the promising natural products, which are often isolated in minute amounts. Consequently, advancements in sampling techniques, structure determination strategies as well as target identification methods represent crucial steps in marine drug discovery [7,8].

It has been presumed that the marine environment was with a scarcity of life forms, but now it has been discovered that there are many marine living organisms with the ability of producing the wide range of compounds with biological effects. Some of the natural products from marine invertebrates are of microbial origin. They have marked effect on the quality and quantity of bioactive compounds and can highly has the efficacy to kill the inhibitors of physiological processes [19]. The marine compounds are assigned to chemical classes such as polyketides, terpenes, nitrogen-containing compounds, or polysaccharides [21]. These natural products has laid different approaches for drug development and serve as the new resources to develop effective and safe drugs as they provides accurate production of target metabolite. They have also accelerated advances in the field of marine biotechnology [13,14]. Natural products from marine compounds played an important function in treatment and prevention of human diseases. In marine invertebrates, so far 7,000 marine natural products have been reported, from sponges 33%, and have been reported to be used in drug discovery [67].

This review will focus the most important compounds of lithistid sponges and their therapeutic and pharmacological values.

Commercially Available Biochemical Probes From Lithistid Sponges
Calcyulin derived from the sponges Discodermia calyx has important key molecules for investigating cellular metabolism [2,62]. Moto purines and congeners are protein phosphatase inhibitors [27]. The complex polyketide swinholide A and bistheonellide A are biologically active metabolites that show nanomolar potent against tumor cells [6,7]. There are actin disrupting compounds derived from lithistid like kabiramide, sphingosine and reidisponginolide, calipectoside but these are not meant for commercial purposes [11,12].

Biological Activity of Lithistid-Derived Compounds
Anti-HIV peptides from the lithistid
The major compound theopalauamide is a bicyclic peptide isolated from lithistid by yeast genetic methodologies in defining mode of action of naturally synthesized products. The theopalauamide is correlated with both anti-HIV and anti-tumor activities [20,47,54]. The theopalauamide is targeted by mevalonate pyrophosphate decarboxylase, an enzyme involved in ergosterol biosynthesis, and this shows that theopalauamide directly interacts with ergosterol. Along with this, a compound theonellamide from
*Theonella* a common species of lithistida also represents a sterol binding agent [15-18]. These both theopalauamide and theonellamide have enough clinical aspects. Many of the cyclic peptides such as papuamides A-D from *Theonella* spp., callipeltin A from *Callipelta* sp., mirbamides A-D from *Siliquaria mirabilis* that inhibit HIV-1 fusion, and homophymines A-D from *Homophymia* sp. have been active to HIV assays, to block viral fusion. Among these compounds, papuamide has high action on HIV. It binds to the HIV and inactivates it. It affects the membrane of the HIV. Cholesterol is a main component of the HIV membrane, and the peptides from the sponges can exert their virucidal activity against cholesterol. Research is going on to find the clinical utilities of these compounds [20,50-52,59].

**TUBULIN ACTIVE AGENTS - LEADS FOR DEVELOPMENT OF CLINICALLY USEFUL AGENTS**

Disruption of microtubule structures is applicable clinically for the discovery of new anticancer drugs. Discodermolide is a polyketide isolated from *D. dissolute* sponges which was initially found to have cytotoxic and immunosuppressive activity. Discodermolide is similar to paclitaxel as it acts through polymerization of tubulin and hyperstabilization of microtubules and is also an antimitotic compound. Discodermolide can induce tubulin polymerization in the absence of GTP and at low temperatures. It has been shown that discodermolide shows its synergistic activity with paclitaxel both *in vitro* and *in vivo* showing that in combination therapeutic rules that would reduce toxicity than the paclitaxel treatment [49,57,58]. Discodermolide was evaluated in phase 1 clinical trials for solid tumor malignancies at the cancer therapy and research center in San Antonio, Texas, using molecular mechanics calculation and NMR methods [25-29]. The various compounds derived from lithistid sponges are illustrated in Fig. 1. Sclerotidermin A derived from *Sclerotiderma nodosum* also a cytotoxic cyclic peptide has the ability to inhibit the tubulin polymerization.
THE LITHISTID IS ARMED WITH MULTIFACETED CHEMICAL ARMAMENTARIUM

A single specimen lithistid possesses numerous compounds with different biological activities. One illustrative example is a Neopeltide family of sponges collected off Jamaica in 442 m water has these following active compounds: dictyosin 1.6, kahramide C acetate 8, neopeltotide-9 [63,64]. The mode of action of all these three is as follows: Dictyostatin is a cytotoxic agent works through polymerization of tubulin and stabilization of microtubules [53,56]. Kahramides acts through inhibition of actin dynamics. Neopeltotide [60,61] has potency again tumor cells and involves in energy production (ATP synthesis). Other organisms collected at the same site had none of these compounds [26-30].

IMPORTANCE OF LITHISTID COMPOUNDS

The derived compounds from lithistid are pollution free and economically viable. They are capable of synthesizing sufficient material to cure cancer and other deadly diseases. They have been used in the discovery and designing of several marine drugs [35-40]. Some of these compounds are also used commercially; for example, calycin A and hemicalycins are anticancer agents and calcycinamides and clavosines are inhibitors of protein phosphatases. Performing various biochemical assays with the lithistid-derived compounds leads to discovery of many other natural products. As derived compounds are natural products, they serve as the better sources for new drugs [40-43]. The compounds isolated and characterized from marine sources have widely used as an alternative for antibacterial, anticancer, antioxidant, and other purposes [34,46,57]. Furthermore, it has been proved that the compounds have more effective therapeutic uses in humans [68].

DRAWBACKS OF LITHISTID COMPOUNDS

The sponge contains three distinct classes of compounds which can target different biochemical processes such as microtubule structure and function, actin and microfilament structure, and ATP production [66]. However, the main drawback is all the other organisms collected at the same site does not have these biochemical processes. Furthermore, the compounds derived from lithistid are produced by associated microorganisms; since the microbes have been involved, it is not clear that whether multiple microbes are involved or does they have any role in the fermentation reactions or any unique production of natural products synthesis is being happened. The other drawback of lithistida is that they grow in more depth and are inhabitants of common regions [65].

CONCLUSION

Based on the diversity of these compounds derived from lithistid and the significant medicinal properties, the lithistid is found to be an important source for developing the natural products with their importance to their biomedical application. It has been also studied that the compounds isolated from the sponges are likely to be produced by the microorganisms, and further, the work is being carried out to culture the microbes and the application has been studied through its different antibacterial, anticoagulant, anti-inflammatory, antiprotozoal, and anthelmintic activities.

Future directions

The different chemical structures and biological activities found in lithistid show that it is an important source of novel metabolites. Continuous exploration of new habitats can also lead to discovery of new chemical utilities of these sponges. Since the sponges occur in both shallow and deep water habitats and act as the tools that allows for exploitation of new collection of sponges. The lithistida remains as an exciting source of natural products which are very useful in biomedical studies and can be act as an important model system for sponge-microbial communities. Improving the pharmacological properties of these derived compounds will be useful in future medical research. This article does not have the conflict of interests.

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