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Biological Activities of the Marine Sponge *Axinella*

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Introduction

Marine natural products have attracted the attention of biologists and chemists on the world over for the last five decades. The ocean is considered to be a source of potential drugs. Covering around 70% of the planet surface, the oceans possess a huge potential for the new discovery[1]. The marine environment exhibits an important biodiversity represented by 34 of the 36 phyla of all globe, with *ca.* of 300000 known species of plants and animals, such as sponges, tunicates, bryozoans, shellfish, bacteria, fish, seaweeds, just to name a few[2]. Large number of compounds with unusual chemical diversity and remarkable biological activity have been isolated from marine organisms up to date. Sponges are the most primitive multicellular, filter feeding, and sesile animals without organised tissue or organ systems. They are a part of the benthic fauna and live in all areas of the marine world, from the shallow coastal seas to the deepest oceans[3]. Since sponges have a wide range of biosynthetic capabilities, they are the dominant source of these compounds[4]. The sponge class Demospongiae is known to produce the largest number and diversity of secondary metabolites isolated from marine invertebrates[5]. Although the functions of these secondary metabolites are largely unknown, there is some evidence that they provide chemical defenses against predators[5-7].

The genus *Axinella* (class Demospongiae, order Halichondrida, family Axinellidae) contains almost 20 species distributed world-wide is known

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to be a source of a variety of metabolites such as bromo compounds, cyclopeptides, polyethers, sterols, and terpenes[8-10].

The focus of this review is to provide information on the biological activities of the marine sponge *Axinella*.

Antifungal Activity

During a search for new antifungal metabolites from marine invertebrates using an the erg6 mutant of the budding yeast *Saccharomyces cerevisiae,* a significant activity was found in the MeOH extract of *A. brevistyla* collected in western Japan. Growth inhibitory activity was determined. Bioassay monitored isolation was afforded four bromopyrole alkaloids which inhibited the growth of the erg6 mutant of *S. cerevisiae* at <1.0, <1.0, 30, and 100 μg/disk[11].

Antimicrobial Activity

First study on the antimicrobial effect of the *Axinella* species was carried on *A. polycapella* and several antimicrobial compounds were isolated[12]. The organic extract of *A. corrugata* was assayed for antibiotic activity against a test panel of marine bacteria and found to be active against a *Bacillus* sp. (NS1: Isolated from necrotic reef sponge *Ircinia strobilina* and NS2: Isolated from necrotic reef sponge *Agelas clathrodes)*, *Vibrio alginolyticus* (HS4: Isolated from healthy reef sponge *Pandaros acanthifolium*), and *Deleya marina* (DM: ATCC). A previously isolated alkaloid stevensine (Fig. 1)[13] exhibited antimicrobial activity at concentrations of 50 to 200 μg/ml against NS1, NS2, HS4, and DM. The zones of inhibition produced by the crude extract of *A. corrugata* however were greater than those for purified stevensine, which was minimally active at 50 μg/ml while the mean concentration of stevensine in the sponge was only 19 μg/ml, suggesting that stevensine might not be the only antibacterial secondary metabolite produced by this sponge[7]. In a study performed on *A. donnani* collected from southeast coast of India, the sponge showed a high antibacterial spectrum inhibiting the growth of all the Gram-positive bacteria tested, however, it showed least activity to the extent of 25% against Gram-negative bacteria[14]. *Helicobacter pylori* is a Gram negative bacterium associated with pepticular and gastric cancer. Imidazo-azolo-imidazole alkaloids called axinellamines (Fig. 1) from Australian marine sponge had a minimum inhibitory concentration (MIC) for bactericidal action against *H. pylori* at 1000 μM[15].

Antiviral Activity

Natural products from terrestrial and marine kingdoms represent an inexhaustable source of compounds with promising antiviral action. In an *in vitro* antiviral activity study of marine sponges collected off the Brazilian coast the aqueous and organic extracts of *Axinella* aff. *corrugata* were tested for anti-herpetic (HSV-1, KOS strain), anti-adenovirus (human AdV serotype 5) and anti-rotavirus (simian RV SA11) activities. The aqueous extract of the sponge presented a promising result for adenovirus (human AdV serotype 5). The adenovirus serotype 5 (AdV-5) is very stable in the enviroment during long periods of time, and it is associated with respiratory infections with no specific treatment[2]. SARS-coronavirus (SARS-CoV) encodes a main protease, 3CL<sup<pro</sup>, which plays an essential role in the viral life cycle and is currently the prime target for discovering new anti-coronavirus agents. In a contribution, a novel red-shifted fluorescense-based assay for 3CL<sup<pro</sup> was developed and a coumarin derivative esculetin-4-carboxylic acid ethyl ester, as anti-SARS agent from *A.* aff. *corrugata* was isolated[16].

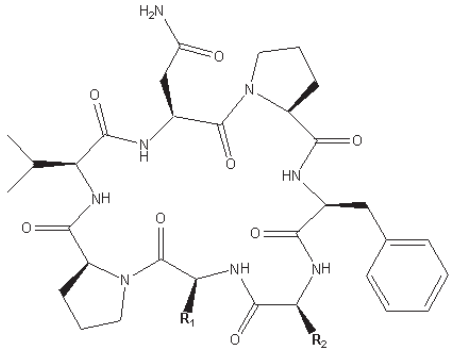
Insecticidal Activity

A study on the tropical marine sponge *A. carteri* demonstrated that the guanidine alkaloids, hymenialdisine and debromohymenialdisine, exhibited insecticidal activity towards neonate larvae of the polyphagous pest insect *Spodoptera littoralis* (LD_{50} 88 and 125 ppm, respectively) when incorporated into artificial diet and offered to the larvae in a chronic feeding bioassay[17].

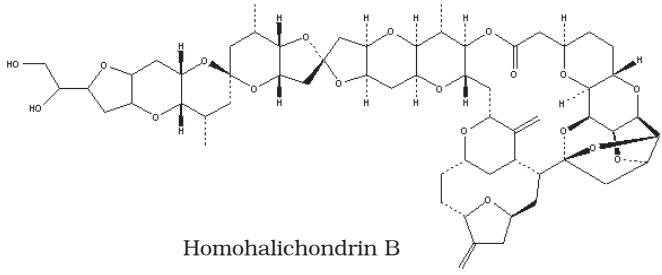
Cytotoxicity

A methylene chloride-2-propanol extract prepared from the specimen of *Axinella* collected in Palau provided a 101 % increase in life span (at 100 mg/kg) against the PS leukemia with ED_{50} 2.5 µg/ml. By means of P 388 lymphocytic leukemia cell line guided bioassay a new PS inhibitory peptide axinastatin 1 (ED_{50} 0.21 µg/ml) was isolated from this sponge (Fig. 1)[18]. Extended bioassay directed separation of the more difficult accesible cytotoxic components of this sponge was resulted in the discovery of two cycloheptapeptides; axinastatins 2 and 3 (Fig. 1). Axinastatin 2 exhibited strong *in vitro* cytotoxicity against the murine leukemia P388 cell line (ED_{50} 0.02 µg/ml), while axinastatin 3 also possessed significant

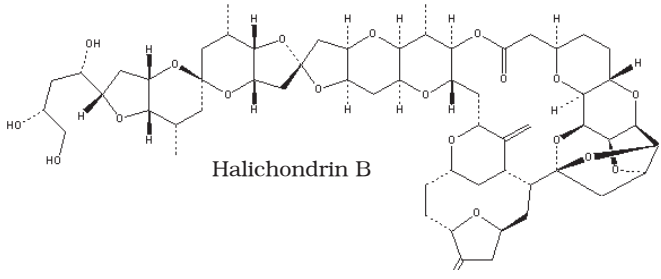
cytotoxic activity (ED_{50} 0.4 µg/ml) against the PS leukemia cell line and showed a higher level of activity than axinastatin 2 against human ovarian, lung, and colon cell lines[19]. As a contiunation of this research marine sponge; *A. carteri* from the Republic of the Comoros was investigated and a cell growth inhibitory cyclopeptide called axinastatin 4, (P 388 lymphocytic leukemia cell line, ED_{50} 0.057 µg/ml) was isolated[20]. *A.* cf *carteri* from the western Indian Ocean yielded a cell (human and murine) growth inhibitory cyclooctapeptide, axinastatin 5 (GI 0.3-3.3 µg/ml)[21]. In another study, the alkaloids; debromohymenialdisine, hymenialdisine, and 3-bromohymenialdisine of *A. carteri* collected from tropical region were tested for their cytotoxicity *in vitro* using L5178y mouse lymphoma cells (Fig. 1). According to data debromohymenialdisine (ED_{50} 1.8 µg/ml) was the most active one, followed by hymenialdisine and 3-bromohymenialdisine (ED_{50} 3.9 µg/ml in both cases)[17]. Two cytotoxic natural products homohalichondrin B and halichondrin B, isolated from an *Axinella* spec. displayed enhanced relative cytotoxicity to the leukemia line HL-60 (TB), ovarian carcinoma line OVCAR-3, the non-small cell lung carcinoma line NCI-H522, the colon carcinoma line KM20L2, and the central nervous system tumor line SF-295 (Fig. 1)[22]. The alkaloids 3-bromomaleimide, 3,4-dibromomaleimide, 12-chloro-11-hydroxydibromoisophakellin, and N-methymanzacidin obtained from *A. brevistyla* (collected in western Japan) exhibited cytotoxicity against L1210 cells with IC_{50} values of 1.1, 0.66, and 2.5 µg/ml, respectively[11]. Two cyclopeptides; axinellins A and B isolated from *A. carteri* were found to exhibit moderate cytotoxic activity against human broncopulmonary non-small-cell-lung-carcinoma lines (NSLC-N6) with IC_{50} values of 3.0 and 7.3 µg/ml, respectively (Fig. 1)[23]. In contrary of all these results a cyclic octapeptide cyclonellin (Fig. 1) from *A. carteri* (Caroline Islands) was evaluated in an *in vitro* cytotoxicity assay that utilized COLO-205 (colon) along with OVCAR-3 (ovarian) human tumor cell lines and reported to be inactive at a high test concentration of 50 µg/ml[24]. In a T47D breast tumor cell-based reporter assay, the crude extract from a South African collection of the marine sponge *Axinella* (5 µg/ml) inhibited hypoxia (1% O_2)-induced HIF-1 activation by 90% without pronounced cytotoxicity (<50%). The extract applied at the same concentration also inhibited an iron chelator (1,10-phenathroline at 10 µM)-induced HIF-1 activation by 50% in T47D cells. Bioassay guided fractionation and isolation procedure of this extract yielded some sodwanone-type triterpenoids that showed activity at various concentra-



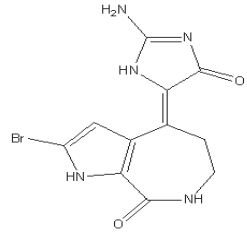
	R_1	R_2
Axinastatin 1	$-CH(CH_3)_2$	$-CH(CH_3)_2$
Axinastatin 2	$-CH_2CH(CH_3)_2$	$-CH(CH_3)_2$
Axinastatin 3	$-CH_2CH(CH_3)_2$	$-CH\begin{matrix}CH_2CH_3\\CH_3\end{matrix}$



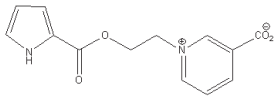
Homohalichondrin B



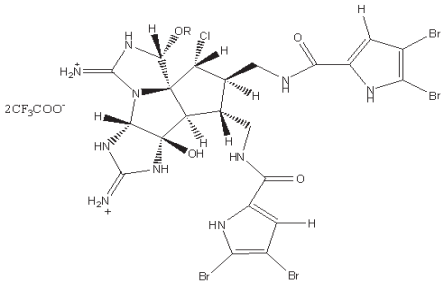
Halichondrin B



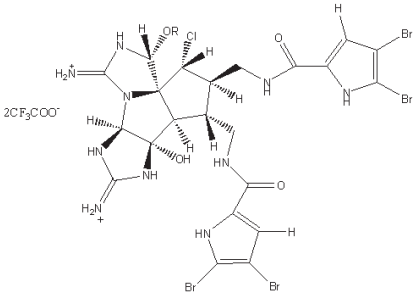
Hymenialdisine



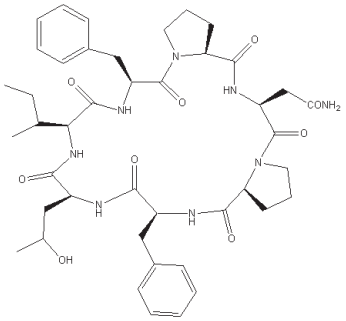
Daminin



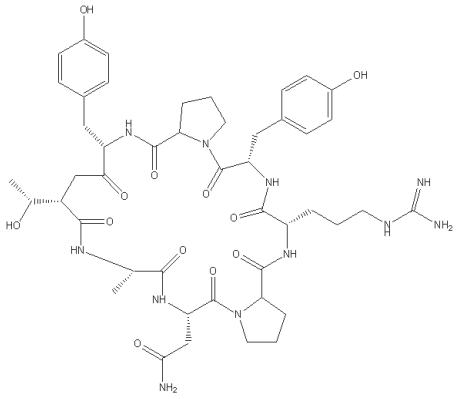
Axinellamine A R= H
Axinellamine C R= CH_3



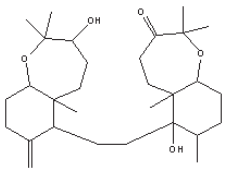
Axinellamine B R= H
Axinellamine D R= CH_3



Axinellin A



Cyclonellin 1



Sodwanone K

Figure 1
Some compounds with biological activites from marine sponge *Axinella.*

tions (Fig. 1)[25]. In a cytotoxicity test using the human lung carcinoma cell line NSCLC-N6, the heptanic-soluble fraction of *A.* cf. *bidderi* showed a significant cytotoxicity (IC_{50} 5 µg/ml). However, the triterpenoids isolated from this fraction displayed a weak inhibition of lung carcinoma cells NSCLC-N6[10]. Some cytotoxic steroids from the Indian Ocean sponge *A.* cf. *bidderi* against human tumoral cell lines namely, prostate (LN-caP), ovary (IGROV-ET), pancreas (PANC1), colon (LOVO) and lung cell lines (NSLC N6-L16) were isolated[26].

A. aff. *corrugata* extracts were tested for their cytotoxicity using sea-urchin eggs. The aqueous extracts of *A.* aff. *corrugata* acted blocking mitosis in the eggs, without causing anomalies or cell lysis[27]. In another study carried on *A.* aff. *corrugata,* the aqueous extract of the sponge at 100 µg/ml concentration was inactive against the HT29 colorectal tumour cell line[1]. Girolline, a 2-aminoimidazole derivative previously isolated from the marine sponge *Peudaxinyssa cantharella,* was also found in *A. brevistyla* collected in western Japan and was shown that cells treated with girolline exhibited G2/M cell cycle arrest[28]. *A. weltneri* col-

lected from subtidal benthic communities off the coast of southern Africa was found as active against esophageal cancer cells[29]. According to Selvin and Lipton *A. donnani* was not active in brine shrimp cytotoxicity assay[14]. Daminin (Fig. 1), an alkaloid isolated from *A. damicornis* collected in the Bay of Calvi displayed no cytotoxic activity (IC_{50} was >40 µg/ml) against several tumor cell lines, namely murine leukemic lymhoblasts L5178y, rat adrenal pheochromocytoma PC12 cells, and human cervix carcinoma HeLa S3 cells[30]. Likely, in a recent study the cell viability tests using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay revealed that the alkaloids isolated from *A. verrucosa* were not toxic at concentrations below 10 µg/ml for PC12, HeLa and L5178y cells. Due to these results they were not considered as cytotoxic compounds[31]. The hexane, chloroform ($CHCl_3$), and methanol (MeOH) extracts prepared from an *Axinella* specimen collected in the Mediterranean coastal zone of Turkey screened for their cytotoxic activity by MTT method. The $CHCl_3$ extract of the sponge was reported to exhibit significant cytotoxic activity against B16 melanoma cells[32].

Telomerase Inhibiting Activity

Telomerase is a ribonucleoprotein enzyme complex that extends telomere lenght by adding hexameric (TTAGGG) repeats onto the telomeric ends of chromosomes. Telomerase activity is essential for the sustained proliferation of most immortal cells, including cancer cells. Its activity is found in more than 90% of cancer cells, but not in most normal cells. Thus, inhibitors of telomerase are a target for anticancer drug discovery. It has been found that the lipophilic extract of the marine sponge *A. infundibula* had significant telomerase inhibitory activity. A bioassay guided isolation study on this sponge afforded a highly sulfated lipopolisaccharide, which inhibited human telomerase with an IC_{50} value of 2.0 µg/ml[33].

Neurological Activities

In a search for bioactive substances from Mediterranean sponges, Aiello et al.[30] reported that a non brominated pyrrole alkaloid, daminin, obtained from *A. damicornis* exhibited a promising neuroprotective activity. *In vitro* tests on rat cortical cell cultures showed that daminin might represent a new therapeutic tool for the treatment of several the central

nervous system (CNS) diseases such as Parkinson's and Alzheimer's diseases. In another study *A. verrucosa* collected from the bay Calvi displayed neuroprotective activity against the agonists serotonin and glutamate *in vitro*. The sponge extract was shown to contain a complex mixture of structurally different brominated pyrrole alkaloids[31].

The bioassay-guided fractionation of the water-soluble extract of *A. carteri* collected in Yap state (Micronesia) afforded a known *N*-methyl-D-aspartic acid (NMDA) type glutamate receptor agonist (2S, 2S)-4sulfooxypiperidine-2-carboxylic acid as an active principle. This compound induced convulsive behaviours in mice upon intracerebroventricular injection with ED_{50} value 20 ± 2.8 pmol/mouse. Radioligand-binding assay using rat cerebrocortical membrane demonstrated that the compound inhibits the binding of the labeled NMDA receptor ligand [^{3}H] CGP39653 at IC_{50} value of 214 ± 20 nM[34].

The aqueous extract of *A.* aff. *corrugata* was tested for neurotoxic activity and found inactive[26].

Anti-inflammatory Activity

Prostaglandins and nitric oxide (NO) are ubiquitous mediator systems which have numerous vascular and inflammatory effects. Production of prostaglandins or NO by the constitutive isoenzymes cyclo-oxygenase-1 (COX-1) or endothelial NO sythase, are implicated in the physological regulation of vascular tone and homeostatic functions. COX-2 and inducible NO synthase are not generally expressed in resting cells, but are induced following appropriate stimulation with proinflammatory agents such as cytokine, lipopolysaccharide and zymosan in numeorus cell types including macrophages. The induction of COX-2 and NO synthase results in the increased synthesis of prostaglandins and NO, which play a key role in the pathophysiology of inflammatory conditions. It was shown that marine diterpenes from the Vanuatu sponge *Axinella* can control nitric oxide and prostaglandin E_2 over production by dual inhibition of the enhanced inducible NO synthase expression and COX-2 activity, in addition with their effect on tumor necrosis factor alpha (TNFα) production[35].

The inflammatory reaction consists of three fundamental processes: -hemodynamic changes, -alterations in vessel permeability and –accu-

mulation of inflammatory cells. The directed migration of inflammatory cells along a chemical gradient is termed chemotaxis. The activation of this process appears to be an important mechanism by which the immune effector cells are located at sites on inflammation. Based on this phenomenon, the organic and aqueous extracts of *A. corrugata* were analyzed for their activity on polymorphonuclear leukocytes chemotaxis. The organic extract of the sponge caused cellular wall damage whereas the aqueous extract showed cytotoxicity, and therefore, they both did not show any antichemotactic activity[1].

Antioxidant Activity

The hexane, $CHCl_3$, and MeOH extracts of the marine sponge *Axinella* collected in the Mediterranean coastal zone of Turkey were found to possess antioxidant properties based on the experiments with DPPH (2,2-diphenyl-1-picryl hydrazyl) which indicated their ability to efficiently scavenge free radicals[32].

Immunostimulatory Activity

Of the two galactose binding hemagglutinins isolated from *A. polypoides,* axinella I was strongly mitogenic for human peripheral blood lymphocytes where axinella II was not. Purified T cells responded strongly and B cells weakly to axinella I. Mitogenic response as monitored by rate of ^3H thymidine incorporation on the third day of culture was specifically inhibited by D galactose, D fucose, raffinose, or 2 deoxy D galactose added within 5 h of the mitogen. Mitogenic response was correlated with degree of lymphocytic agglutination. Axinella I depressed ^3H thymidine incorporation induced by phytohemagglutinin or Concavalin A (Con A), an effect reversible by D galactose. The findings suggested that axinella I had two antagonistic effects on human lymphocytes as mitogenic activation and depressive activity resulting from depletion of essential galactose moieties[36]. In the frame of an European Union (EU) project extracts of different polarity from sponges, ascidians and cnidarians, as well as several pure compounds have been screened for immunomodulating activities. In a murine cell culture-based screening, the marine sponge *Axinella* exhibited activity. Bioassay guided isolation led to the substance hymenamide C, a cyclic peptide that inhibited the lymphocyte proliferation significantly[37]. A glycosphingolipid obtained from *A. damicornis* collected

in Sorrento (Italy) was shown to possess immunostimulatory effect by the splenoycyte proliferation tests[38].

Other Biological Activities

Reintamm et al.[39] reported that a novel nucleosidase enzymatic activity (converting adenosine-5'-triphosphate into adenine and ribose-5-triphosphate) was discovered in the sponge *A. polypoides* collected near the Kalymnos Island (Greece).

The aqueous, dichloromethane/methanol and ethyl acetate extracts obtained from *A.* aff. *corrugata* were tested for their haemolytic activity. The aqueous extract was found inactive while the dichloromethane/methanol extract was positive in concentrations up to 500 µg/ml ES (0.5% mice erythrocytes suspension) where the ethyl acetate extract was positive in concentrations from 50 to 499 µg/ml ES[27].

Axinella spp. collected from Andaman (India) showed diuretic activity in mice having LD_{50} 825 mg/kg [40].

A. andomonensis collected from the Red Skin Island, South Andaman coastal zone displayed cardiovascular activity in mice with LD_{50} 46.4 mg/kg[40].

Conclusion

In this review the genus *Axinella* and some of the secondary metabolites from *A.* spec. have been evaluated for their various biological activities including antimicrobial, cytotoxic, anti-inflammatory and antioxidant activities. The potential of leads from *Axinella* continues to grow, particularly in the area of cytotoxicity, inflammatory and CNS-related conditions.

The information summarized here provides a means to understand biological activitiy studies of the genus.

Summary

Biological Activities of the Marine Sponge *Axinella*

The genus *Axinella* (class Demospongiae, order Halichondrida, family Axinellidae) contains approximately 20 species, distributed world-wide is known to be a source of a variety of secondary metabolites such as bromo compounds, cyclopeptides, polyethers, sterols, and terpenes. In

this review the genus *Axinella* and some of the compounds isolated from this genus have been evaluated from the view point of biological activities including antimicrobial, cytotoxic, anti-inflammatory and antioxidant activities.

Key words: Axinella, Axinellidae, Halichondrida, marine sponge, biological activity

Özet

Axinella Cinsi Deniz Süngerinin Biyolojik Aktiviteleri

Yaklaşık 20 türle tüm dünyada yayılış gösteren *Axinella* cinsi (sınıf Demospongiae, takım Halichondrida, familya Axinellidae) bromlu bileşikler, siklopeptidler, polieterler, steroller ve terpenler gibi değişik sekonder metabolitlerin bir kaynağı olarak bilinmektedir. Bu derlemede, *Axinella* cinsi ve içerdiği bazı maddeler, antimikrobiyal, sitotoksik, antienflamatuvar ve antioksidan aktiviteler gibi biyolojik aktiviteleri açısından değerlendirilmiştir.

Anahtar Kelimeler: Axinella, Axinellidae, Halichondrida, deniz süngeri, biyolojik aktivite

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