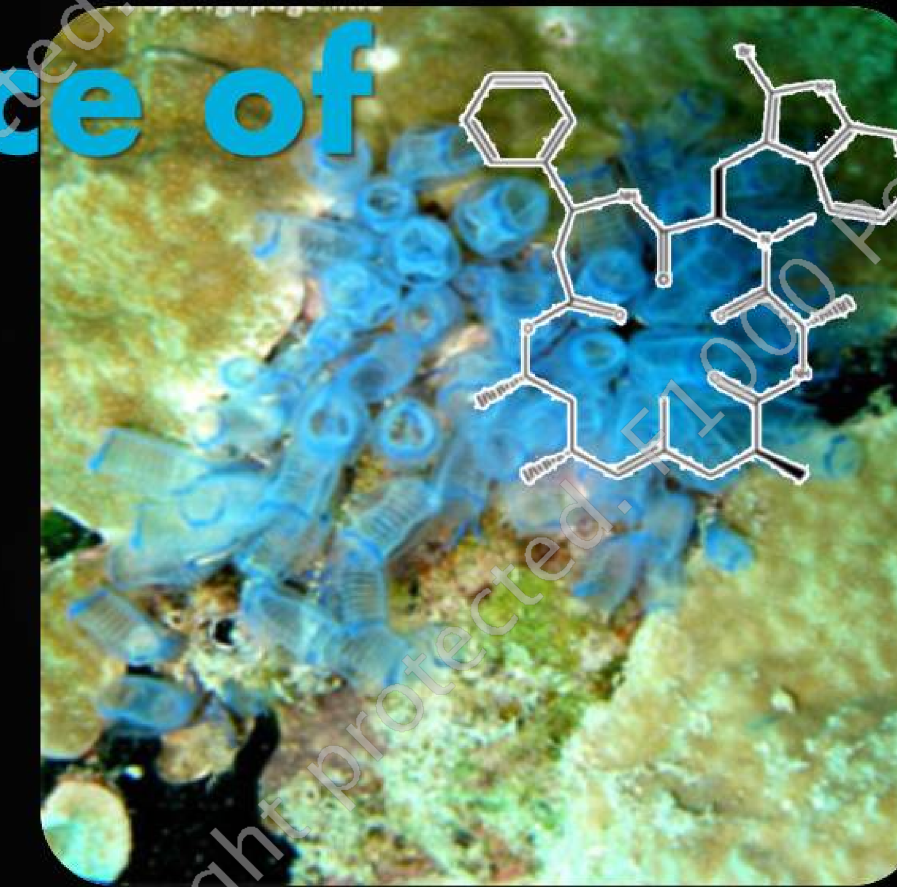
Marine sponges: A potent source of anticancer metabolites



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Abstract

The search for pharmaceutically active compounds from natural sources is well established. With oceans covering 70% of the surface of the earth, coupled with the large and varied biodiversity of the marine environment, the oceans remain a largely unexplored, but extremely promising source of new drug candidates. Approximately half of the novel marine natural products reported in the literature are biologically active. This occurrence can be contributed to the reliance of sessile, soft-bodied marine invertebrates on chemical defense for survival, as many lack the physical defense mechanisms of movement and camouflage. Among the most promising sessile marine organisms in this aspect are marine sponges. More than 15.000 marine products have been described up to now in which sponges are champion producers, concerning the diversity of products that have been found. They are responsible for more than 5300 different products and every year hundreds of new compounds are being discovered. Most bioactive compounds from sponges can be classified as antiinflammatory, antitumour, immuno- or neurosurpressive, antiviral, antimalarial, antibiotic or antifouling. The chemical diversity of sponge products is remarkable. In addition to the unusual nucleosides, bioactive terpenes, sterols, cyclic peptides, alkaloids, fatty acids, peroxides, and amino acid derivatives (which are frequently halogenated) have been described from sponges. The bmarine sponges continue to attract attention as rich sources of structurally novel anticancer secondary metabolites

Marine Chemical Ecology

Several marine organisms are sessile and soft bodied, then the question will arise: how do these delicate looking simple sea creatures protected themselves from predators and pathogens in the marine environment? While answering this interesting ecological question, researchers found that marine organisms have defensive chemical weapons (secondary metabolites) for their protection. Intensive evolutionary pressure from competitors, that threaten by overgrowth, poisoning, infection or predation have armed these organisms with an arsenal of potent chemical defense agents. They have evolved the ability to synthesize these chemical weapons or to obtain them from marine microorganism.

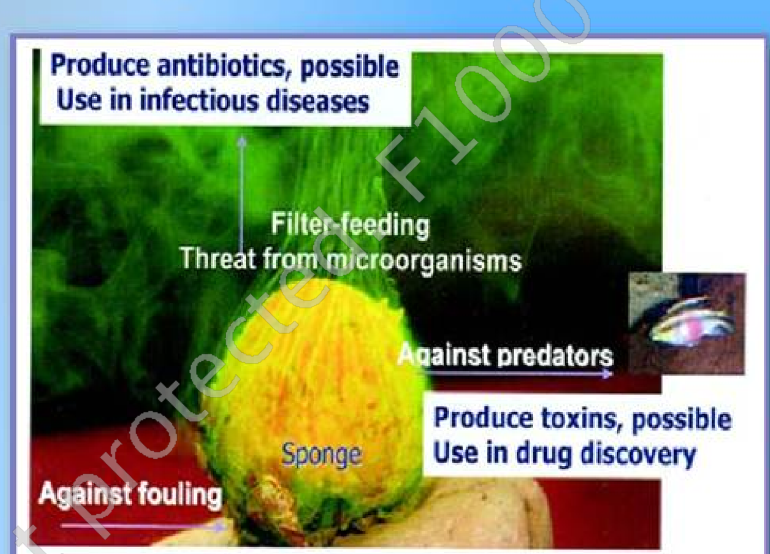
Bioactive compounds from sponges

Sponges are known as prolific sources of bioactive compounds that can potentially be used to treat various human diseases (Faulkner, 2000). The isolation of bioactive metabolites from sponges, including a number of structurally unusual and biologically interesting compounds with a wide range of activity, has been extensively reviewed. The discovery of the new nucleosides spongethymidine and spongeuridine in the Caribbean sponge *Tethya crypta* has inspired the development of a series of synthetic nucleosides that are now commercially available (Newman and Cragg, 2004). Several bioactive compounds from sponges have passed the preclinical stage of the drug testing process. One of the significant sponge derived metabolites in phase I of clinical trials since 2004 is polyketide discodermolide from the Caribbean sponge *Discoderma dissolute* (Gunasekera et al., 1990).

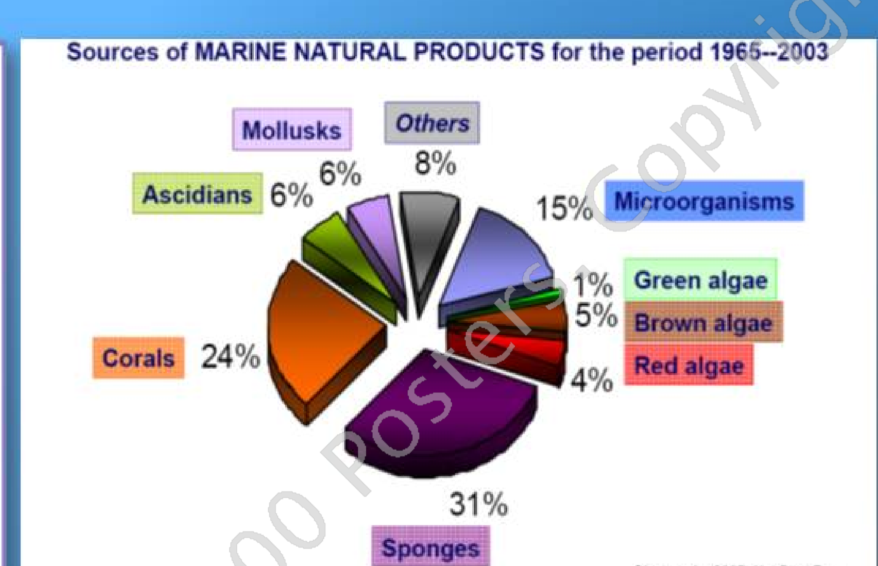
Selected examples of marine natural products which are currently in market or in clinical trials

Product	Source	Application area	Status
Ara-A	Marine sponge	Antiviral	Market
Ara-C	Marine sponge	Anticancer	Market
Cephalosporins	Marine fungi	Antibiotic	Market
Conotoxins	Cone snail	Chronic pain	Phase I/II/III
GTS21	Nemertine worm	Alzeimer's disease	Phase I/II
LAF389	Sponge	Cancer	Phase I
Bryostatin-1	Bryozoan	Cancer	Phase II
Yondelis™	Sea squirt	Cancer	Phase II/III
Dolastatin-10	Sea slug	Cancer	Phase II
ILX651	Sea slug	Cancer	Phase I
Cemadotin	Sea slug	Cancer	Phase II
Discodermolide	Sponge	Cancer	Phase I
HTI286	Sponge	Cancer	Phase I
Aplidin™	Sea squirt	Cancer	Phase II
Squalamine lactate	Shark	Cancer	Phase II
IPL512602(steroid)	Sponge	Inflammation, Asthma	Phase II

Discodermolide has been shown to inhibit the proliferation of human cells by arresting the cell cycle in G2- and M-phase, the same mechanism of action of the major anticancer drug pacilitaxel. However, discodermolide binds microtubules with an even higher affinity than pacilitaxel (ter Haar et al., 1996). Another sponge-derived anticancer compound in phase I of clinical trials is the glycolipid KRN7000 from the marine sponge Agelas mauritianus (Hayakawa et al., 2003). Moreover, halichondrin B, an unusual polyether macrolide originally discovered from the Japanese marine sponge *Halichondria okadai*, is highly promising as anticancer agents

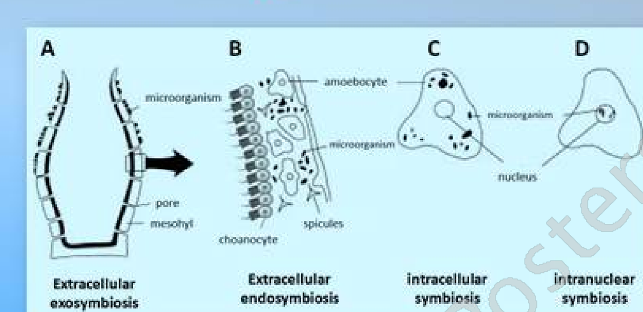


Sponges produce cytotoxic compounds, possible use in cancer treatment



Sponges are the highest marine organisms in natural products production

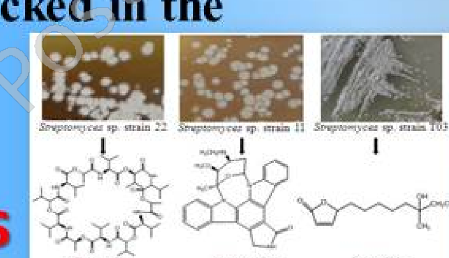
Sponge-associated microorganisms



Schematic diagram of symbiotic relationships between sponges and microorganisms. A, extracellular exosymbiont; B, extracellular endosymbiont; C, intracellular symbiont; and D, intranuclear symbionts (Lee et al., 2001)

Sponges harbor diverse and complex assemblages of microorganisms i ncluding bacteria, cyanobacteria, diatoms and archaea. Sponge-associated bacteria can constitute up to 60% of the sponge biomass being densely packed in the intercellular and intracellular matrix.

Bioactive compounds from bacterial symbionts of sponges



Many metabolites isolated from marine sponge closely resemble bacterial natural products or belong to substance classes typical for these microorganisms, such as complex polyketides synthase (PKS) and nonribosomal peptide synthase (NRPS). Several brominated bioactive compounds and other aminoacid derivatives are present in complex structures such as cyclic peptides, polymere alkylpyridinum, sesquiterpenequinones, onamides, mycalamides, nucleotides to macrolides, porphyrins, terpenoids to aliphatic cyclic peroxides and sterols are also other important cytotoxic secondary metabolites.

Examples of sponge anticancer compounds in clinical trials and use

Vidarabine, an anti-viral drug (used against the Herpes simplex encephalitis virus), and Ara-C, an anti-cancer drug, isolated from the sponge *Tethya crypta.*

Halichondrin B was originally isolated from the sponge *Halichondria okadai*, but was also found in the sponge *Lissodendoryx sp.* The compound has pronounced anti-cancer activity. A synthetic derivative thereof, called E7389, is currently in clinical trials against lung cancer.

Discodermolide, found in the sponge *Discodermia dissoluta*, is in clinical trials against solid tumors.

Agelasphins from the sponge *Agelas mauritianus* have pronounced antitumor and immunostimulatory properties. A synthetic derivative is in clinical trials for cancer immunotherapy.

Psammaplin A is a compound present in several species of the order *Verongida*, but was first found in *Psammaplysilla sp.* It was a lead structure for the synthetic anticancer compound NVP-LAQ824 and for the antibiotic against the bacterium Staphylococcus aureus.

Designed by:
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