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## MARINE SPONGES AS PHARMACY

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## ABSTRACT

Marine sponges have been considered as a drug treasure house with respect to great potential regarding their secondary metabolites. Most of the studies have been conducted on sponge's derived compounds to examine its pharmacological properties. Such compounds proved to have antibacterial, antiviral, antifungal, antimalarial, antitumor, immunosuppressive, and cardiovascular activity. Although, the mode of action of many compounds by which they interfere with human pathogenesis have not been clear till now, in this review not only the capability of the medicinal substances have been examined in vitro and in vivo against serious pathogenic microbes but, the mode of actions of medicinal compounds were explained with diagrammatic illustrations. This knowledge is one of the basic components to be known especially for transforming medicinal molecules to medicines. Sponges produce a different kind of chemical substances with numerous carbon skeletons, which have been found to be the main component interfering with human pathogenesis at different sites. The fact that different diseases have the capability to fight at different sites inside the body can increase the chances to produce targeted medicines.

**KeyWords :** Sponge Medicine-Natural Product -Inflammation - virus

### INTRODUCTION

The relationship between sponges and medicines goes back to Alexandrian physicians and was thoroughly describes by the Roman historian Plinius. Physicians used sponges that were saturated with iodine to stimulate coagulation of the blood, or with bioactive plant extracts to anesthetize patients. Sponges were of soaked with pure wine and put on the left part of the chest in case of heartaches and soaked in urine to treat bites of poisonous animals. Plinius recommended the use of sponges against sunstrokes, and they were used against all kinds of wounds, bone fractures, dropsy, stomach aches, infectious diseases, and testicular tumors, or even as im- plants after breast operations. At least since the 18th century, Russian, Ukrainian, and Pol- ish physicians have used a freshwater sponge they call Badiaga for the treatment of patients. The dry powder of this sponge is rubbed on the chest or back of patients with lung diseases or on the sore places in cases of foot and leg aches such as rheumatism. Oficjalski dis- covered that Badiaga is not really one sponge, but mixtures of several freshwater sponges that differ depending on the region. In Poland it consisted of powder of *Euspongilla lacustris*, *Ephydatia fluviatil-* is, and *Meyenia muelleri*, while the Russian Badiaga was a mixture of *Euspongilla lacustris*, *Ephydatia fluviatilis*, *Spongilla fragilis*, and *Carterius stepan-* owi. He suggested that the high iodine concentration in all sponge species gives rise to the wholesome effect of Badiaga. At present Stodal, syrup containing roasted *Spongia officinalis*, is used for homeopathic treatment of dry and asthmatic cough in the Western world (Stodal, 2003). Pharmaceutical interest in sponges was aroused in the early 1950s by the discovery of a nucleosides spongothymidine and spongouridine in the marine sponge *Cryptotethia crypta*. These nucleosides were the basis for the synthesis of Ara-C, the first marine-derived anticancer agent, and the antiviral drug Ara-A (Proksch et al., 2002). Ara-C is currently used in the routine treatment of patients with leukemia and lymphoma. One of its fluorinated derivatives hasalso been approved for use in patients with pan- Correspondence to:

### SPONGE PRODUCTS

#### 1)Antiinflammatory Compounds:

Acute inflamma-tions in the human body can result from microbialinfection, physical damage, or chemical agents. The body reacts by changing the blood flow, increasing the permeability of blood vessels, and allowing the escape of cells from the blood into the tissues (Tan et al., 1999). Chronic inflammation of the skin or joints may severely damage the body if it leads to psoriasis or rheumatic arthritis (Pope et at., 1999). Sponges have proved to be an interesting source of antiin- flammatory compounds. Manoalide, one of the first sesterterpenoids to be isolated from a marine sponge (*Luffariella variabi-* lis), was found to be an antibiotic (De Silva and Scheuer, 1980) and an analgesic (Mayer and Jacobs, 1988). In addition, its antiinflammatory properties

have been studied extensively (Bennet et al., 1987). The antiinflammatory action is based on the irre-versible inhibition of the release of arachidonic acid from membrane phospholipids by preventing the enzyme phospholipase A2 from binding to the membranes (Glaser et al., 1989). A rise in the intra- cellular arachidonic acid concentration would lead to upregulation of the synthesis of inflammation mediators as prostaglandins and leukotrienes. Phospholipase A2 inhibition has been re-corded for many sesterterpenes from sponges of the order Dictyoceratida, but also for bis-indole alkaloidssuch as topsentin (Jacobs et al., 1994). The mecha-nism by which they affect the inflammation process is different from commonly used nonsteroidal anti-inflammatory drugs. Only a few sponge-derived terpenoids have been found to inhibit lipoxygenase, another enzyme that is involved in the inflamma- tory response (Carroll et al., 2001). The antiinflammatory sponge products are selec- tive inhibitors of specific enzymes of a range of dis-eases, like psoriasis or rheumatic arthritis. The currently used nonsteroidal antiinflammatory drugs often fail to control the disease and present important side effects such as risk of gastrointestinal bleeding and renal complications (De Rosa, 2002).

### Example:

- Manoalide - Dictoceratida
- Subersic Acid – Subarea Species
- Topsentin – Topsentia Genitrix

### 2)Antitumor compound:

A number of

isolated sponge compounds are inhibitors of protein kinase C (PKC). PKC inhibitors have attracted interest worldwide, as there is evidence that too high levels of PKC enzyme are involved both in the patho- genesis of arthritis and psoriasis (owing to regula-tion of phospholipase A2 activity), and in tumor development (Bradshaw et al., 1993; Yoshiji et al., 1999). PKC is believed to be the receptor protein of tumor-promoting phorbol esters, and PKC inhibi- tors prevent binding of carcinosarcoma cells to the endothelium (B. Liu et al., 1991). Glycosylation of the receptors, and especially the presence of fucose residues, plays an important role in the binding of carcinosarcoma cells and leukocytes to the receptors in the endothelium (Springer and Lasky,1991). Fucosyltransferase inhibitors, such as the octa and nonaprenylhydroquinone sulfates that were isolated from a *Sarcotragus* sp. (Wakimoto et al., 1999), may therefore be promising candidates for controlling inflammatory processes such as arthritis or for combating tumor growth. In addition to PKC inhibitors and fucosyl trans- ferase inhibitors, numerous anticancer molecules with a different mode of action have been discovered in marine sponges.

These compounds can be divided in 3 classes:

- (1) nonspecific inhibitors of cell growth;
- (2) spe-cific inhibitors of cancer cells; and
- (3) inhibitors of cancer cells of a certain type of cancer (as the aforementioned PKC inhibitors).

Many nonspecific cell growth inhibitors have been discovered in sponges. They are valuable for treating cancer under certain conditions, but they also affect the division of healthy cells. Therefore, their applications are limited, depending on their specific characteristics. The cytoskeleton is an interesting target for cancer therapy, as the micro- tubules and microfilaments are involved in cellular organization during cell division. A number of ado-ciasulfates (triterpenoid hydroquinones) from a *Haticlona* sp. were the first inhibitors of the kinesin motor protein to be discovered. These toxins are believed to inhibit the protein by binding to the microtubule binding site, “locking up” the proteins motor function, and thereby blocking cell division (Blackburn et al., 1999). In

In addition to these triterp- enoid hydroquinones, a number of potent microtu- buleinterfering compounds have been discovered in marine sponges, such as halichondrin B (Bai et al., 1991), spongistatin (Bai et al., 1993), discodermolide (Ter Haar et al., 1996), laulimalide (Moobeny et al., 1999), peloruside A (Hood et al., 2002), and dict- yostatin (Isbrucker et al., 2003). Other metabolites, such as latrunculin A from *Latrunculia magnifica* (Coue et al., 1987) and swinholide A from *Theonella swinhoei* (Bubb et al., 1998), disrupt the polymeri- zation of actin. Actin which is the key element of the microfilaments, and it can block many cellular processes including cell division. Spongiacidin B (Inaba et al., 1998) and faspalyisin (Soni et al., 2000) are examples of sponge- derived metabolites that in- hibit cell division by inhibition of cyclindependent kinase 4, which leads to arrest of cells in the G1 phase. Other metabolites, such as mycalamide (Burres and Clement, 1989) and aragusterol (Fukuoka et al., 2000), disturb cell division by inhibition of protein synthesis. Neoamphimedine (De Guzman et al., 1999) and elenic acid (Juagdan et al., 1995) inhibit the development of tumors by blocking topoisom- erase II, the nuclear enzyme which makes transient DNA breaks that are required for replication (L.F. Liu and Chen, 1994) the production of the natural mucus that protects the

### Examples:

- BRS1 – Calcarous sponge
- Spongistatin 1 – Spongia Species
- Haligramides A and B – Haliclona nigra

### 3) Immunosuppressive compounds:

Immunosuppressive Compounds. In addition to their potential for treatment of cancer, nitric oxide synthetase inhibitors downregulate T-cells are, suppressing the immune system, and they diminish the fierceness of migraine attacks (Griffith and Gross, 1996). Immune system suppression is desired in cases of hypersensitivity to certain antigens (e.g., allergies) or organ transplantations. Patients who receive a donor organ need life-long medication to prevent rejection by the immune system, and for that reason it is extremely important that these medicines are very specific suppressors. Therefore there is a continuous demand for new immunosuppressives. A number of new molecules with immunosuppressive activity, which interfere at different points of the immune response have been discovered in marine sponges. Three polyoxygenated sterols from a *Dysidea* sp. from Northern Australia are selective immunosuppressive compounds that inhibit the binding of interleukin 8 (IL-8), a cytokine that attracts neutrophils into an area of tissue injury, to the IL-8 receptor (Leone et al., 2000). The simplexides from the Caribbean sponge *Plakortis simplex* are a group of immunosuppressive glycolipids that inhibit proliferation of activated T cells by a noncytotoxic mechanism (Costantino et al., 1999). Pateamine A, from a *Mycale* sp., inhibits the production of IL-2 (Romo et al., 1998) and thereby the activation of resting T cells and B cells to a lesser extent. Contignasterol from *Petrosia contignata* (Burgoyne and Andersen, 1992) inhibits allergen-induced histamine release from rat mast cells (Takei et al., 1994) and from guinea-pig lung tissue in vitro (Bramley et al., 1995), and the activation of eosinophils into airways in guineapigs and could be used to treat asthma (Langlands et al., 1995)

### Examples:

- Simplexides – plakortis Simplex
- Polyoxygenated Sterols – Dysidea Species
- Pateamine A- Mycale Species

#### 4) Cardiovascular Agent:

In addition to regulators of the white blood cells, a number of sponge derived molecules have been found to interfere with other blood-related diseases such as thrombosis, atherosclerosis, or diabetes. The process of blood coagulation is triggered by a complex proteolytic cascade that leads to the formation of fibrin. Thrombin is a serine protease that cleaves a peptide fragment from fibrinogen, which then leads to the generation of fibrin, a major component of blood clots (Shuman et al., 1993). Cyclotheonamide A, isolated from a *Theonella* sp. (Fusetani et al., 1990), represents an unusual class of serine protease inhibitors and is a potential drug for the treatment of thrombosis (Maryanoff et al., 1993). Eryloside F from *Erylus formosus* was found to be a potent thrombin receptor antagonist (Stead et al., 2000). Thrombin receptor activation is likely to play a key role not only in arterial thrombosis but also in atherosclerosis (Chackalamannil, 2001). Atherosclerosis starts with damage to the endothelium and subsequent deposition of fats, cholesterol platelets, cellular waste products, calcium, and other substances in the artery wall. These may stimulate endothelial cells to produce a vascular cell adhesion molecule that results in further buildup of cells and shrinkage of the arterial diameter (Zapolska-Downar et al., 2001). Halichlorine from *Halichondria okadai* is an inhibitor of the expression of vascular cell adhesion molecule 1 (Kuramoto et al., 1996) and may thus impede atherogenesis (Arimoto et al., 1998). Callyspongynic acid, isolated from *Callyspongiatruncata*, is an  $\alpha$ -glucosidase inhibitor (Nakao et al., 2002).  $\alpha$ -Glucosidase inhibitors interfere with the hydrolysis of glycogen, keeping the glucose concentration in the blood at a lower level, and can be used to treat patients with diabetes (Lebovitz, 1992).

#### Examples:

- Cyclotheonamide – *Theonella* species
- Eryloside F- *Astrophorida*
- Halichlorine – *Halichondrida okadai*

#### 5) Neurosuppressive Compound:

Keramidine, isolated from an *Agelas* sp. (Nakamura et al., 1984), is an example of a number of neurosuppressive compounds that have been isolated from marine sponges. It is a serotonergic receptor antagonist and blocks serotonin-mediated neural communication. Several different serotonin receptors have been identified. They are related to (1) platelet aggregation, and may therefore be useful against thrombosis (Ruomei et al., 1996); (2) smooth muscle contraction (Garcia-Colunga and Miledi, 1996); (3) vomiting, owing to their presence in the gastrointestinal tract (Lang and Marvig, 1989); (4) and most interestingly, may function as antidepressant drugs in the brain (Nagayama et al., 1980). Dysiherbaine from *Dysidea herbacea* (Sakai et al., 1997) is a potent excitatory amino acid that causes seizures by interfering with the L-glutamate based neurotransmitter communication and may provide a lead compound in therapeutical agents for disorders (Sakai et al., 2001)

#### Examples:

- Keramidine – *Agelas* species
- Dysiherbaine- *Dysidea herbacea*

#### 6) Muscle relaxants:

Disturbances in neuromuscular communication resulting from stress cause permanent muscle activation (Lundberg, 1995; Edgar et al., 2002). In addition to the above-mentioned centrally acting muscle relaxants, which mediate neuromuscular communication, peripherally acting muscle relaxant may be used for local muscle relaxation. They are applied for relief of strokes, or during intubations and surgery (Frakes, 2001). 1 - Methylguanosine from *Tedania digitata* (Quinn et al., 1980) and xestospongins C, which was isolated from a *Xestospongia* sp. (Gafni et al., 1997), are examples of muscle relaxants that discovered in sponges. Xestospongins C is a potent inhibitor of the inositol 1,4,5-triphosphate (IP<sub>3</sub>) receptors and the endoplasmic-

reticulum Ca<sup>2+</sup> pumps (De Smet et al., 1999) and inhibits IP<sub>3</sub>-induced increase in the oscillatory contraction of muscles (Miyamoto et al., 2000).  $\beta$ -Adrenoreceptor agonists, such as S1319 isolated from a *Dysidea* sp. (Suzuki et al., 1999), have utero-relaxant properties, which can be therapeutically used for the preterm delivery of infants (Dennedy et al., 2002), and are widely used as antiasthmatic drugs (Suzuki et al., 1999). However, owing to their low selectivity  $\beta$ -adrenoreceptor agonists may have severe side effects such as arterial hypertension, coronary heart disease, and tachycardia (Borchard, 1998). Therefore, there is continued interest in finding more selective  $\beta$ -adrenoreceptor agonists such as S1319 **Examples:**

- 1-methylisoguanosine – *Tedania digitata*
- Xestospongins C- Xestospongia species
- S1319 – *Dysidea* species

### 7) Antiviral compounds :

Sponges are also a rich source of compounds with antiviral properties. The high number of HIV-inhibiting compounds discovered does not reflect greater potential of sponges to fight AIDS compared with other viral diseases, but rather the interest of many researchers. The strong focus on screening for anti-HIV activity has led to discovery of numerous compounds, but the mechanism of inhibition is still poorly characterized. Papuamides C and D (Ford et al., 1999), haplosamates A and B (Qureshi and Faulkner, 1999), and avarol (Muller et al., 1987), which has also been patented as antipsoriasis (Muller et al., 1991), are examples of HIV-inhibiting compounds from different sponges. Avarol is one of the few compounds for which the mechanism by which it inhibits progression of HIV infection is more or less known. In vitro and animal data indicate that avarol combines useful properties of an increased humoral immune response, as IgG and IgM production is significantly increased, and interference with the posttranscriptional processes of viral infection (Muller et al., 1987). Avarol inhibits HIV by almost completely blocking the synthesis of the natural UAG suppressor glutamine transfer tRNA. Synthesis of this tRNA is upregulated after viral infection, and it is important for the synthesis of a viral protease, which is necessary for viral proliferation (Muller and Schroder, 1991). Low concentrations of only 0.9 and 0.3  $\mu$ M avarol resulted in 80% and 50% inhibition of virus release from infected cells, respectively (Schroder et al., 1991), while uninfected cells were highly resistant against avarol (Muller et al., 1985; Kuchino et al., 1988). Furthermore, it was shown that the avarol derivatives, 6 $\beta$ -hydroxy avarol and 3 $\beta$ -hydroxy avarone (Figure 6), were very potent inhibitors of HIV reverse transcriptase. This enzyme has a key role in the early stages of HIV infection and is a specific target for antiviral drugs, as it is responsible for converting the viral genomic RNA into proviral double-stranded DNA, which is subsequently integrated into the host chromosomal DNA (Loya and Hizi, 1990). In addition to their applications to treat diabetes,  $\alpha$ -glucosidase inhibitors, such as callispongic acid, are potentially broad-based antiviral agents. They disturb protein glycosylation and cause some viral envelope proteins to be misfolded, which leads to arrest of these proteins within the endoplasmic reticulum, where protein folding takes place. It has been demonstrated that alteration of the glycosylation pattern of HIV, hepatitis B virus, and bovine viral diarrhoea virus by  $\alpha$ -glucosidase inhibitors attenuates viral infectivity (Ratner et al., 1991; Mehta et al., 1998).

A very different class of virus inhibitors that has been found in many different sponges are 2 $\beta$ -5 $\beta$  oligoadenylates (2–5A), which are involved in the interferon-mediated response against a wide range of viruses in mammals. The antiviral action is based on the activation of a latent endoribonuclease that prevents viral replication by degradation of its mRNA as well as cellular RNA (Kelve et al., 2003). For many other antivirals, the mechanism of inhibition is still unclear, but they are active against range of viruses. Hamigeran B from *Hamigera tarangaensis*, for example, showed 100% in vitro inhibition against both the herpes and polio viruses (Wellington et al., 2000), and the weinbersterols A and B from *Petrosia weinbergi* exhibited in vitro activity against feline leukemia virus, mouse influenza virus, and mouse corona virus (Sun et al., 1991; Koehn et al., 1991). In general, antiviral molecules from sponges do not give protection against viruses, but they may result

in drugs to treat already infected persons. In addition, broad-based antiviral agents such as 2-5A and  $\alpha$ -glucosidase inhibitors may be useful in cases of sudden outbreaks of (unfamiliar) viruses like SARS and Ebola.

### Examples:

- Dragmacidin F – *Halicortex* species
- Haplosamates A and B – *Xestospongia* species
- Weinbersrerols A and B – *Petrosia weinbergi*

### 8)Antibiotics and fungicides:

With respect to antibiotics and fungicides, similar multiresistance problems have concerned physicians for a long time. Many new molecules with antibiotic properties are discovered every year, but in marine sponges their ubiquity is remarkable (Table 8). An early screening by Burkholder and Ruetzler (1969) revealed that 18 of 31 sponges tested showed antimicrobial effects, of which some were very strong against a range of gram-positive and gram-negative bacteria. The added value of some new sponge-derived antibiotics was shown by the inhibitory effect of arenosclerins A–C from *Arenosclera brasiliensis* on 12 antibiotic-resistant bacteria isolated from a hospital (Torres et al., 2002). Fungicides that are currently used are less diverse than antimicrobials, and the use of many of them is restricted because of toxic effects to humans, animals, and plants (Nakagawa and Moore, 1995; Rahden-Staron, 2002). It remains to be demonstrated whether antifungals like topsentiasterols D and E from *Topsentia* sp. (Fusetani et al., 1994), acanthosterol sulfates I and J from an *Acanthodendrilla* sp. (Tsukamoto et al., 1998) or the macrolide leucascandrolide A from the calcareous sponge *Leucascandra caveolata* (D'Ambrosio et al., 1996) will have different characteristics than the fungicides that are currently used, but the fact that they are produced by eukaryotic organism (if not produced by a symbiont) may imply that they are less toxic to other nonfungal eukaryotes.

### Examples:

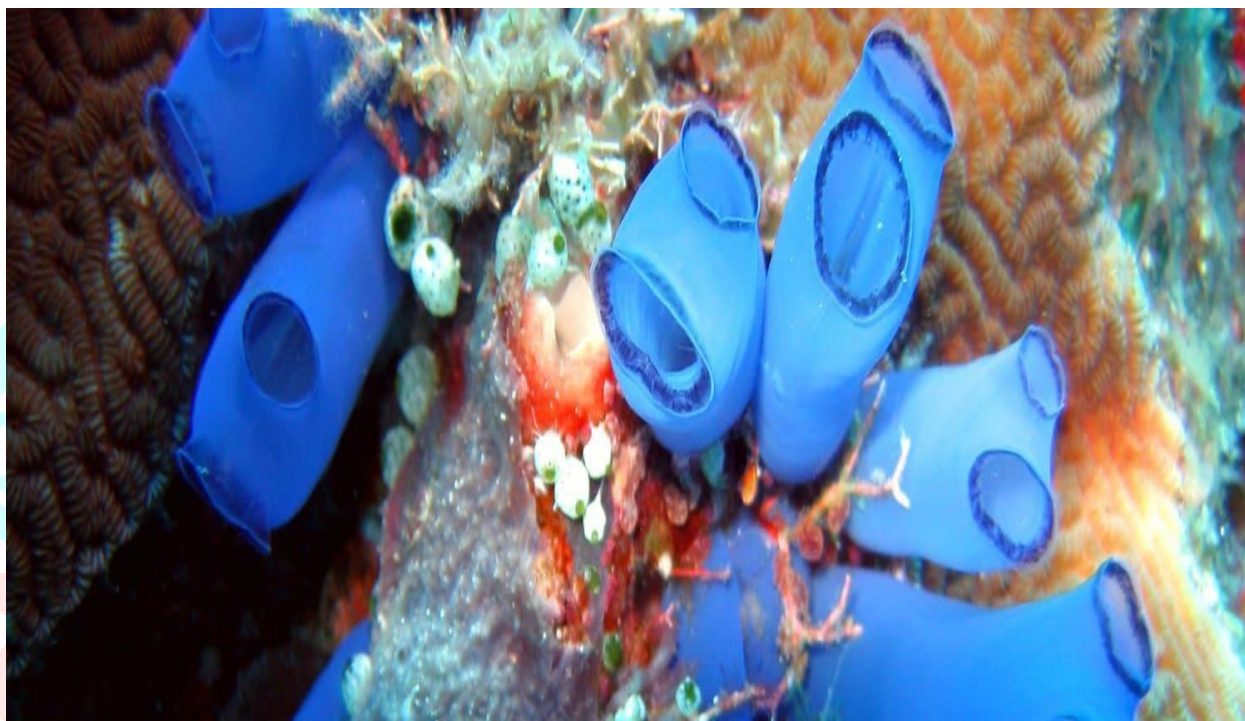
- Discodermins B, C, and D – *Lithistida*
- Topsentiasterol sulfates A-E – *Topsentia* species
- Acanthosterol sulfates I and J – *Acanthodendrilla* species

### BIOLOGICAL CHARACTERISTIC OF SPONGE

Sponges, the most primitive multicellular animals, consist of comparatively independent cells characterized by fluidity and differentiation potential. Most sponge biological activities (such as feeding, reproduction, and gas exchange) are completed and controlled by current (Wu, 1995).

For example, flagellated choanocytes in choanocyte chambers can remove food particles from waters. Sponges are sessile creatures distributed in marine or freshwater from deep sea to the coast (Liu, Zheng, 1997 ; Hooper, 2002), and are dominant among marine species in number, especially, deep-sea species. But knowledge of their biological and ecological characteristics is so far very limited. Sponges differ from other multicellular animals in not having organs and true tissues. Sponges are composed of highly differentiated mesohyl containing spicules and specialized cells in different shapes and functions (Simpson, 1983; Jones, 1994; Osinga, 1999). Sponges are classified by the shape of the spicules (Kerr, Lelly-Borges, 1994; Diaz, van Soest, 1994; Rodrigo et al., 1994; Hooper, 2002) or by the shape of the aquiferous system, a network of channels and chambers through which water flows (Wu, 1995). With the development of molecular biology, some scientists proposed to classify the sponge by gene expression (SoleCava, 1994; Muller, 2001). Currently, the most used criterion is according to the spicule, by which sponges are divided into four classes, *Calcarea*, *Demospongiae*, *Hexactinellida* and *Archaeotyatha*. Asexual and sexual reproduction are known in sponges. Most sponges multiply by sexual reproduction. Sponges produce sperms and eggs in different time. Sperms caught by sponges

are turned into eggs with the aid of archeocytes. Larvae are reproduced during the sexual stage and released into the sea. The development and hatching of encapsulated gemmules are highly ordered in asexual processes (Pronzato and Manconi, 1994; RichelleMaurer and Degoudenne, 1994), which was observed in winter in freshwater spongillids and more recently in marine species. When weather is good, the bud or gemmule would turn into sponges.



## CONCLUSION

Marine sponges produce an enormous array of antitumor, antiviral, antiinflammatory, immunosuppressive, antibiotic, and other bioactive molecules that can affect the pathogenesis of many human diseases. The relationship between the chemical structures of the secondary metabolites from sponges and the diseases they affect is usually not obvious. Different components affect the targeted disease by different mechanisms (e.g., microtubule stabilization or interaction with DNA to combat tumors). Moreover, inhibitors of transcription may be effective against both cancer and viral diseases. To make things more complex, there are many relations between, for instance, inflammation, cancer, and viral infections via the immune system, which plays a key role in certain responses of the body to these diseases. Chronic inflammation of the lungs by cigarette smoke often leads to lung cancer (Ohwada et al., 1995) and cervical and liver cancer can follow chronic inflammation caused by papilloma viruses (Smith-McCune et al., 1996) and hepatitis B and C viruses, respectively (Zhu et al., 1997). In addition, limited activity testing (e.g., only on cell growth inhibition and not on antiviral properties) yields an incomplete overview of the actual properties of the metabolites. Finally, for many bioactive molecules from sponges, the exact mode of action and their origin (sponge or symbiont) are still unclear. Most bioactive metabolites from sponges are inhibitors of certain enzymes, which often mediate or produce mediators of intracellular or intercellular messengers involved in the pathogenesis of a disease



As this is usually a cascade of reactions inside the cell or tissue, many enzymes in the cascade are targets for potential therapy. The different enzymes in the cascade can be structurally completely different proteins; therefore, it is not surprising that a wide range of metabolites can be used for the treatment of one disease.

### MARINE SPONGES IRRITATION SYMPTOMS

- 1) Initially, a stinging or itchy , prickly sensation is felt.
- 2) Later, burning , pain , blisters , joint swelling and severe itching may develop.
- 3) In cases with large body exposure to certain sponges , patients may develop fever , chills ,dizziness , muscle cramps and nausea.

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