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Review

A study of malaria resistance and the urgent need to discover new antimalarials

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Malaria, which is caused by multiplication of the protozoan parasite *Plasmodium falciparum* in erythrocytes, is a major health problem in many southern countries. There is an urgent need to discover new antimalarials, due to the spread of chloroquinine resistance and the limited number of available drugs. Among marine invertebrates, Porifera (sponges) are potential source of novel bioactive compounds to provide future drugs against malaria, cancer and a range of viral diseases. A number of sponge-derived antimalarials have been discovered during the last decade. The compounds are mostly nitrogen containing ones (proteins, pyridines, tyrosine-based metabolites, alkaloids, indoles and amides) and also non-nitrogenous compounds (terpenes, polyketides and polysaccharides).

Keywords: Malaria, *Plasmodium falciparum*, porifera, marine sponges, bioactive compounds, antimalarial compounds.

INTRODUCTION

Malaria is the most important parasitic disease, leading to annual death of about one million people (Penet et al., 2007). The difficulty of obtaining an antimalarial vaccine along traditional lines, because of the highly adaptive character of the malaria parasite, prompts a ceaseless need for new drugs. The characterization of the kinome of the human malaria parasite *Plasmodium falciparum* has revealed profound divergences, at several levels, between protein kinases of the parasite and those of its host (Doerig et al., 2007). The malarial parasite, *P. falciparum* is genetically diverse and it has multiple independent origins of mutations in genes that confer resistance to widely used antimalarial drugs (Mu et al., 2003). About 500 million new cases reported annually is a challenge to vaccines or drug therapy (Joshi and Viswanathan, 2006).

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Drug resistance accompanied by lack of progress in the development of vaccines or resistant reversal agents has further aggravated the situation. The increasing number of multidrug- resistant *Plasmodium* strains warrants exploration of new antimalarials of natural origin especially marine sponges.

Marine sponges as pharmacy

Pharmaceutical interest in sponges was aroused in the early 1950's by the discovery of a number of unknown nucleosides: spongothymidine and spongouridine in the marine sponge *Cryptotheca crypta* (Bergmann and Feeney, 1950, 1951). More than 15.000 marine products have been described up to now (Lit, 1999; Faulkner, 2000, 2001, 2002). Sponges are champion producers, concerning the diversity of products that have been found. They are responsible for more than 5300 different

Table 1. Chemistry and activity of bioactive compounds from marine sponges. Chemistry: (k). terpenes:diterp:diterpenes, sester:sesterterpene,sesquit:sesquiterpene, (l). polyketides,(m). e,sesquit : sesquiterpene, (l). polyketides, (m).

Drug class	Compound	Chemistry	
Antimalarial	Papuanoate	Terpene[K]	D'mbrosio et al., 1998
"	Kalihinol A	Diterp[K]	Miyaoka *etal.*, 1998
"	Oroidin	Pyrrol[m]	Konig et al., 1998
Anticoagulent	Halisulfate Suvanine	Sester[k]	Kimural et al*.,* 1998
Antifungal	Cyclolithistid A	Depsipm	Clark et al., 1998
Antifungal	Spongistatin	Maacrolide[l]	Pettit et al., 1998
Antifungal	Acanthosterols	Sterols[K]	Tsukamoto et al*.,* 1998
Antiplatelet	Mycaloilide-B	Macroilde[l]	Sugidachi et al., 1998
Antiviral	Frondosin	Sesqui[t]	Hallock et al., 1998
Antiviral	Adociavir	Protein[m]	O'Keefe et al., 1998
Antitumor	Elenic acid	Alkylphenol	Juagdan et al., 1995
"	Callystatin A	Polyketide	Kobayashi et al., 1997
	Axinellins A& B	Cyclic peptide	Randozzo et al*.,* 1998

Nitrogen- containing compounds: depsi:depsipeptide.

products and every year hundreds of new compounds are being discovered (Faulkner, 2000, 2001, 2002).

Most bioactive compounds from sponges can be classified as anti-inflammatory, antitumour, immuno- or neuro-suppressive, 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 (Tramper, 1999).

Marine sponges have a potential to provide future drugs against important diseases, such as malaria, cancer and a range of viral diseases (Aneiros and Garateix, 2004). Of 10,000 marine sponges, 11 genera are known to produce bioactive compounds, and only three genera (*Haliclona, Petrosia* and *Discodemia*) are known to produce anti-malarial, anticancer and ant- inflammatory compounds. The marine sponges continue to attract attention as rich sources of structurally novel bioactive secondary metabolites (Table 1).

Production of bioactive compounds

Marine animals in general and marine invertebrates in particular are promising organisms for synthesis of novel bioactive compounds. This is an adaptation strategy to thrive in the extreme environmental conditions of the sea and as a defense strategy to escape from predators by the marine invertebrates especially soft bodied animals like sponges (Werner et al., 2004).

Focusing on sponges, a conceptual progress occurred with the study of Thakur et al. (2003), who suggested that marine animals and their symbiotic microorganisms (bacteria and fungi) produce an array of bioactive compounds against foreign attackers. A recent concept is the notion that symbiosis is driven by environmental biotic constraints. The host (sponge) synthesizes bioactive compounds that provide protection against attacking microorganisms or eukaryotes, e.g., acetylenic compounds (Richelle-Maurer et al., 2003). The symbiotic bacteria or fungi produce secondary metabolites that act as antibiotics, *e.g.*, cribrostatin (Pettit et al., 2000), or as cytostatic agents, e.g. sorbicillactone-A (Bringmann and Lang, 2003). Functionally, these compounds act only as defense molecules. Another functional class of secondary metabolites of sponges and their associated microorganisms play a dual role: they are involved in defense as well as in the activation of pathways crucial for self-defense (Werner et al., 2004). The sponges possess molecules similar to and homologous with those of the innate and adaptive immune systems of higher metazoa (Muller et al., 1999).

Antimalarial compounds

The compound manoalide from a Pacific sponge has spawned more than 300 chemical analogs, with a significant number of them going to clinical trial as antimalarial agents (Jha and Zi-rong, 2004). A number of cyclic peroxides have been isolated from the marine sponges belonging to the genera *Mycale, Chondrilla, Sigmosceptrella, Plakortis, Plakiinastrlla, Latrunculia, Diacarnus* and *Xestospongia*. Phloedictins extracted from the reef sponge *Oceanapia fistilosa* are antimalarial in nature. The phloedictins belong to a family of alkaloids and are composed of a lateral poly-N chain and a variable- length of carbon chain. There are 3 groups –A, B, C based on the structu-

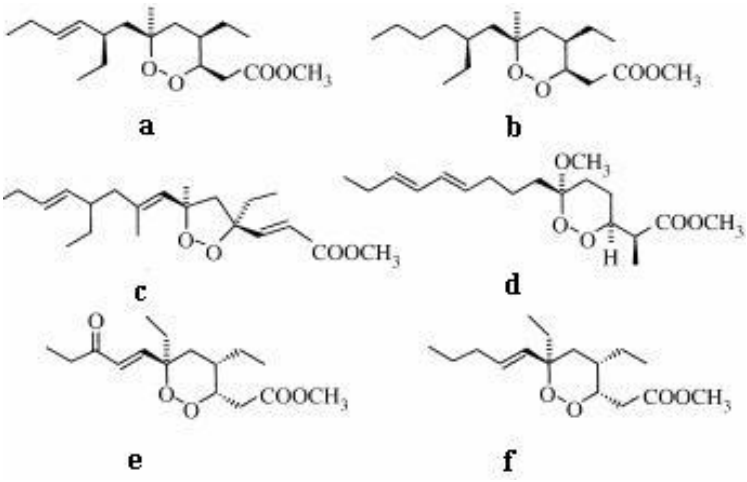

Figure 1. Chemical structures of the cycloperoxides under study and related compounds. Plakortin (a) dihydroplakortin (b) plakortide E (c) peroxyplakoric acid B3 (d) plakortide I (e) and plakortide L (f).

Table 2. Antimalarial products derived from sponges.

Compound	Class of compound	Sponge sp. & Order	Reference
Manzamine-A	Manzamine alkaloid Diterpene isocyanates Isothiocyanates & isonitriles Norditerpenoid & Norsesterterpenoid Endoperoxides	*Haliclona* sp./Haplosclerida *Cymbastela hooperi* **/** Halichondrida *Diacarnus levii*/ Poecilosclerida	Ang et al*.,* 2001 Konig et al*.,* 1996 D' Ambrosio et al*.,* 1998
Axisonitrile-3	Sesquiterpenoid isocyanide	*Acanthella klethra*,/ Halichondrida	Angerhofer et al., 1992
Kalihinol-A	Isonitril-containing kalihinane diterpenoid	*Acanthella* sp../ Halichondrida	Miyaoka et al*.*, 1998

tural variation that can occur in the lateral chains of variable length and degree of unsaturation. Phloedictins types B and C carry an additional sulfurated poly-N chain. Twenty- five different compounds that belong to phloedictins are known from *O. fistilosa.* Simple monocyclic 1,2 - dioxane derivatives exhibit antimalarial activity due to the functional group at C-3, in addition to the endoperoxide bond. Contrastingly plakortin and dihydroplakortin, both lacking functionality at C-3, have significant antimalarial activity (Figure 1) (Ernesto Fattorusso et al., 2002).

A number of sponge-derived antimalarial compounds have been discovered during the last decade (Table 2). Sponge derived compounds are mostly nitrogen-containing ones (*ie.* proteins, peptides, pyridines, tyrosine-based metabolites, alkaloids, indoles and amides) and also non-nitrogenous compounds (terpenes, polyketides and polysaccharides) (Aleejandro and Virgina, 2000). Kalihinol- A from an *Acanthella* sp. (Miyaoka et al., 1998) and a number of terpenoid isocyanates, isothiocyanates and isonitriles from *Cymbastela hooperi* (König et al., 1996) display *in vitro* antimalarial activity against *P. falciparum* . Also a number of free carboxylic acids from *Diacarnus levii* were used as precursors to yield a number of new cyclic norditerpene peroxides after esterification. These epidioxy-substituted norditerpenes and norsesterterpenes displayed selective activity against both chloroquine-sensitive and chloroquine resistant *P. falciparum* strains (D' Ambrosio et al., 1998). Manzamines are the most promising antimalarial compound that has been discovered in a number of sponges (Sakai et al., 1986; Ang et al., 2000; Youssaf et al., 2002). This antimalarial effect of manzamine-A is due to an enhanced immune response (Ang et al., 2001). Youssaf et al., 2002). This antimalarial effect of manzamine-A is due to an enhanced immune response (Ang et al., 2001).

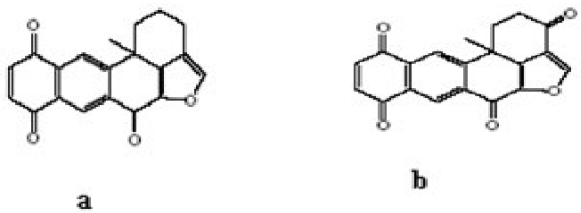

Figure 2. Chemical structures of a, Xestoquinone and b. Halenaquinone.

Sponges produce mainly noresterpene and norditerpene peroxide acids and some of them such as sigmosceptrellin-A, and its C-3 epimer sigmosceptrellin-B, are shown to possess *in vitro* activity against *Plasmodium* (El Sayed et al., 2001) . The sponges of the Plakinidae family (*Plakinastrella* and *Plakortis*), which are prominent members of both Caribbean and Indo-Pacific coral reefs produce polyketide metabolites containing six or five - membered 1,2-dioxygenated rings. Starting from the isolation of the parent compounds such as plakortin (Higgis and Faulkner, 1978) and chondrillin (Wells, 1976), *Plakortis* sponges have been recognized as prolific sources of 1,2-dioxide, 1,2- dioxolane and 3-alkoxy-1,2-dioxine (Peroxyketal) compounds. The red sea sponges *Sigmosceptrella prianos* in South African Plakortis are known to produce Norseterpene and sigmosceprellin (Rudi et al., 1993).

Some of the recent papers reporting on the antimalarial activity of simple monocyclic 1,2-dioxane derivatives have appeared. Synthetic and natural 3-alkoxy-1,2-dio-xine and 3-alkoxy- 1,2-dioxiane (peroxyketal) derivatives shown to possess good antimalarial activity (Murakami. et al., 2002). In both classes of these molecules the substituent at position 3 could partly mimic the non-peroxidic oxygen atom of artemisinin. Good antimalarial activity was also recently reported for a 1,2-dioxane derivative substituted at position 3 with an , unsaturated ketone, and interestingly, the corresponding molecule lacking the carbonyl function was completely inactive (Hu et al., 2001). Studies of Kawanishi et al. (2004) show the structure and activity relationship of antimalarial spongean peroxides and the authors synthesized several analogues concerning with the 6- methoxyacetyl moiety and the 3-pentyl residue in methyl l2-(3-methoxy-3-pentyl-1,2-dioxan-6-yl) acetate and then evaluated for antimalarial activity.

A new bioactive sesterterpene and antiplasmodial alkaloids were isolated from the marine sponge *Hyrtios* cf. *erecta* in Fiji (Kirsch et al., 2000). Anthony et al. (2001) reported the inhibition of heme detoxification processes underlies the antimalarial activity of terpene isonitrile compounds from marine sponges. Most promising tetrahydropyrrolo[1,2-] pyrimidinium, bis-indole, and C11–N5 alkaloids reported from sponges particularly, mixed-biogenesis -galactosyl ceramides from sponges (Pietra, 2006). Dominique et al. (2006) identified antimalarial potential of xestoquinone (Figure 2), a protein kinase inhibitor isolated from a Vanuatu marine sponge Xestospongia sp. Xestoquinone showed *in vitro* antiplasmodial activity against a FCB1 *P. falciparum* strain with an IC50 of 3 lM and a weak selectivity index.

Manzamines are a structurally unique group of -carboline alkaloids isolated from several marine sponge species of the Indian Ocean and the Pacific Ocean.

Manzamine-A was initially isolated from *Haliclona* sp. (Sakai et al., 1986) but has been subsequently found in other genera of marine sponges, including Pellina, Pachypellina, Xestospongia, Ircina, and Amphimedon (Kenny et al., 2000) . In addition, more than 30 other com-pounds structurally related to manzamine-A have been isolated from sponges and characterized; these inclu-de 8-hydroxymanzamine-A and the ketone derivative manzamine-F. The origin, isolation, and chemistry of various manzamines with the complete synthesis of manzamine-A being recently reported (Wright et al., 1996). Ang et al. (2000) isolated manzamine-A, , - carboline alkaloid in several marine sponges, inhibiting the growth of the rodent malaria parasite *Plasmodium berghei in vivo*. They also suggested the manzamine- A and 8-hydroxymanzamine-A, as promising new antimala-rial agents.technical status of different methods to pro-duce sponge.

Conclusion

The rich diversity in bioactive compounds from sponges has provided molecules that interfere with the pathogenesis of a disease at many different points, which increase the chance of developing selective drugs against specific targets. Marine sponges have provided many examples of novel secondary metabolites that possess varied chemical status and potent antimalarial activity. Marine natural products provide a novel and rich source of chemical diversity that can contribute to design and development of new and potentially useful anti-mala-rial agents. Unfortunately, these secondary metabolites are usually present in trace amounts, and natural stocks are too small to sustain the development of widely available medicines. The development of ways to obtain large quantities of the secondary metabolites is therefore currently the most important quest. The current metabo-lite is to study the feasibility of pharmaceuticals from sponges at a large- scale. A combined approach of (genetically modified) bacterial fermentation (to produce a precursor molecule) followed by a limited number of chemical steps to produce molecules that are derived from sponge chemicals will probably be the most successful method to develop medicines from sponge metabolites that are present in low concentrations.

The available data demonstrates that the marine ecosystem is not only productive to discover antimalarial entities but it is also a tool to identify new cellular targets for therapeutic intervention. A better understanding of the molecular determinants of therapeutic response will help identify patients at risk for severe toxicities or those more likely to respond to a given therapeutic regimen, thus paving the way for customized antimalarial therapy to become a reality in the near future. A proactive interaction between researchers, the pharmaceutical sector and government regulating agencies is crucial to the incorporation of this challenging new tool in clinical medicine.

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REFERENCES

Abel Aneiros and Anoland Garateix, (2004). Bioactive peptides fromma-rine sources: pharmacological properties and isolation procedures. J. Chromatogr. B 803: 41-53.

Alejandro MS, Mayer, Virgina, KB Lehmann (2000). Marine pharma-cology in 1998: Marine compounds with Antibacterial, Anticoagulent, Antifungal, Antinflammatory, Anthelminitic, Antiplatelet and Antiviral activities; with actions on the cardiovascular, endocrine, immune, and nervous systems: and other Miscellaneous mechanisms of action. The Pharmacol. 42: 62-69.

Ambrosio D, M Guerriero, A Deharo, E Debitus, C Munoz, V Pietra F (1998). New types of potentially antimalarial agents: epidioxy-substituted norditerpene and norsesterpenes from the marine sponge Diacarnuslevii. Helv. Chim. Acta 81: 1285-1292.

Amrita Rudi, Kashman, (1993). Three new cytotoxic metbolities from the marine sponges. J. Nat. Prod. 56 (10): 27-1830.

Ang KKH, Holmes MJ, Kara UAK (2001). Immune-mediated parasite clearance in mice infected with Plasmodium berghei following treatment with manzamine A. Parasitol. Res. 87: 715-721.

Ang, KKH, Holmes, MJ, Higa, T, Hamann, MT, Kara, UAK (2000). In vivo antimalarial activity of the beta-carboline alkaloid manzamine A. Antimicrob. Agents Chemother. 2000: 1645-1649.

Anthony D. Wright, Huiqin Wang, Marion Gurrath, Gabriele M. König, Gulcan Kocak, Gregory Neumann, Paul Loria, Michael Foley and Leann Tilley. (2001), Inhibition of Heme Detoxification Processes Underlies the Antimalarial Activity of Terpene Isonitrile resonance spectroscopy reveals an impaired brain Compounds from Marine Sponges. J. Med. Chem., 44 (6): 873 -885.

Bergmann W, Feeney RJ (1951). Contributions to the study of marine products. XXXII The nucleosides of sponges. I. J. Org. Chem. 16: 981-987

Bergmann W, Feeney RJ (1950). The isolation of a new thymine pentoside from sponges. J. Am. Chem. Soc. 72: 2809-2810.

Bringmann G, Lang G (2003. Full absolute stereostructures of natural products directly from crude extracts: the HPLC-MS/MS-NMR-CD 'triad'. In: WEG Müller, editor. Sponges (Porifera). Marine Molecular Biotechnology Berlin: Springer. pp. 89–116.

Doerig, Christian, Meijer and Laurent, (2007). Antimalarial drug discovery: targeting protein kinases. Expert Opin. Ther. Targets, 11 (3): 279-290.

Dominique Laurent, Vale´rie Jullian, Arnaud Parenty, Martine Knibiehler, Dominique Dorin, Sophie Schmitt, Olivier Lozach, Nicolas Lebouvier, Maryvonne Frostin, Fre´de´ric Alby,d Se´ verine Maurel, Christian Doerig, Laurent Meijerf and Michel Sauvain. (2006b). Antimalarial potential of xestoquinone, a protein kinase inhibitor

Dominique Laurent and Francesco Pietra, (2006a). Antiplasmodial Marine Natural Products in the Perspective of Current Chemotherapy and Prevention of Malaria. A Rev. , Marine Biotechnol. 8 (5): 33-447.

El Sayed KA, Haman MT, Hashish NE, Shier WT, Kelly M, Khan AA (2001). Antimalarial, antiviral, and antitoxoplasmosis norsesterpene peroxide acids from the Red Sea sponge Diacarnus erythraeanus. J. Nat. Prod. 64: 522–4.

Ernesto Fattorusso, Silvia Parapini, Claudio Campagnuolo, Nicoletta Basilico, Oraziomtaglialatela-Scfati and Donatella Taramelli, (2002). Activity against *Plasmodium falciparum* of cycloperoxide compounds obtained from the sponge Plakortis simplex. J. Antimicrob. Chemother. 50: 883- 888.

F Kelly, M Franzblau SG, Zhang F, Peraud O, Hill RT, Hamann MT (2002). 12,34-Oxamanzamines, novel biocatalytic and natural products from manzamine producing Indo-Pacific sponges. Tetrahedron 58: 7397-7402.

Faulkner DJ (2002). Marine natural products. Nat. Prod. Rep. 19: 1-48.

Faulkner DJ (2000). Marine natural products. Nat. Prod. Rep. 17: 7-55.

Faulkner DJ (2001). Marine natural products. Nat. Prod. Rep. 18: 1-49.

Higgs MD, Faulkner DJ (1978). Plakortin, an antibiotic from Plakortis halichondrioides. J. Org. Chem. 43: 3454–34547.

Hu JF, Gao HF, Kelly M, Hamann MT (2001). Plakortides I-L, four new cyclic peroxides from an undescribed Jamaican sponge Plakortis sp. (Homosclerophorida, Plakinidae). Tetrahedron 57: 9379–83.

isolated from a Vanuatu marine sponge Xestospongia sp. Bioorganic & Med. Chem. 14: 4477–4482.

Joshi A.A, Viswanathan CL (2006). Recent Developments in Antima-larial discovery. Anti-Infective Agents in Med. Chemi. 5 (1): 105-122.

Juagdan EG, Kalindindi RS, Scheuer PJ, Kelly-Borges M (1995). Elenic acid, an inhibitor of Topoisomerase II, from a sponge, Plakinastrella sp. Tetrahedron Lett. 36: 2905-2908.

Kawanishi M, Kotoku N, Itagaki S, Horii T, Kobayshi M (2004). Struc-ture-activity relationship of anti-malarial spongean peroxides having a 3-methoxy-1,2-dioxane structure. Bioorg. Med. Chem. 15: 12(20): 5297-307.

Kenny K H Ang, Michael J Holmes, Tatsuo Higa, Mark T Hamann, Ursula AK Kara (2000). In Vivo Antimalarial Activity of the Beta-Carboline Alkaloid Manzamine A. Antimicrob. Agents Chemother. 44(6): 1645–1649.

Kobayashi M, Higuchi K, Murakami N, Tajima H, Aoki S (1997). Callystatin A, a potent cytotoxic polyketide from the marine sponge, Callyspongia truncata. Tetrahedron Lett. 38: 2859-2862. MarinLit (1999). A marine literature database maintained by the Marine Chemistry Group, University of Canterbury, Christchurch, New Zealand.

König GM, Wright AD, Angerhofer CK (1996). Novel potent antimalarial diterpene isocyanates, isothiocyanates, and isonitriles from the tropical marine sponge Cymbastela hooperi. J. Org. Chem. 61: 3259-3267.

Miyaoka H, Shimomura M, Kimura H, Yamada Y, Kim HS, Wataya Y (1998). Antimalarial activityof kalahinol A and new relative diterpenoids from the Okinawan sponge, Acanthella sp. Tetrahedron 54: 13467-13474.

Mu Jianbing, Ferdig Michael T, Feng Xiaorong, Joy Deirdre A, Duan Junhui, Furuya Tetsuya, Subramanian G, Aravind L, Cooper Roland A, Wootton John C , Xiong Momiao, Su Xin-zhuan (2003) .Multiple transporters associated with malaria parasite responses to chloroquine and quinine.. Molecular Microbiology 49 (4): 977-989.

Müller WEG, Blumbach B, Müller IM (1999). Evolution of the innate and adaptive immune systems: relationships between potential immune molecules in the lowest metazoan phylum (porifera) and those in vertebrates. Transplantation 68: 1215-1227.

Murakami N, Kawanishi M, Itagaki S, Horii T, Kobayashi M (2002). New readily accessible peroxides with high anti-malarial potency. Bioorg. Med. Chem. Lett. 12: 69–72.

Penet MF, Kober F, Confort-Gouny S, Le Fur Y, Dalmasso C, Coltel N, Liprandi A, Gulian JM, Grau GE, Cozzone P.J. and Viola, A. (2007). Magnetic metabolic profile in mice resistant to cerebral malaria infected with Plasmodium berghei. J. Biol. Chem, March15.http://www.jbc.org/cgi/doi/10.1074/jbc.M608035200.

Pettit GR, Knight JC, Collins JC, Herald DL, Young VG (2000). Antineoplastic agent 430 isolation and structure of cribostatins 3, 4 and 5 from the Republic of Maldives Cribrochalina sp. J. Natl. Prod. 63: 793–8.

Pettit RK, McAllister SC, Pettit GR, Herald CL, Johnson JM, Cichacz ZA (1998). A broad-spectrum antifungal from the marine sponge Hyrtios erecta. Int. J. Antimicrob. Agents 9: 147-152.

Rajeev Kumar Jha, Xu Zi-rong (2004). Biomedical compound sfrom marine organisms. Mar. Drugs, 2: 123-146.

Randazzo A, Dal Piaz F, Orrù S, Debitus C, Roussakis C, Pucci P, Gomez-Paloma L (1998). Axinellins A and B: New proline-containing antiproliferative cyclopeptides from the Vanuatu sponge Axinella carteri. Eur. J. Org. Chem. 11: 2659-2665.

Richelle-Maurer E, Gomez R, Braekman JC, Van de Vyver G, Van Soest RWM, Devijver C (2003). Primary cultures from the marine sponge Xestospongia muta (Petrosiidae, Haplosclerida). J. Biotechnol. 100: 169–176.

sa Kirsch, Gabriele M. Köng, Anthony D. Wright, and Ronald Kaminsky, (2000). A New Bioactive Sesterterpene and Antiplasmodial Alkaloids from the Marine Sponge Hyrtios cf. erecta, Nat. Prod. 63 (6): 825 - 829.

Sakai R, Higa T, Jefford CW, Bernardinelli G (1986). Manzamine A, a

novel antitumor alkaloid from a sponge. J. Am. Chem. Soc. 108: 6404-6405.

Thakur NL, Hentschel U, Krasko A, Anil AC, Müller WEG (2003). Antibacterial activity of the sponge Suberites domuncula and its primmorphs: potential basis for chemical defense. Aqua. Microbiol. Ecol. 31: 77–83.

Tramper Ir J (1999). Cultivation of Marine Sponges. Detmer Sipkema. Process Engineering Group, Wageningen University, The Netherlands. p. 184**.**

Tsukamoto S, Matsunaga S, Fusetani N, Van Soest RWM (1998). Acanthosterol sulfates A-J: Ten new antifungal steroidal sulfates from a marine sponge Acanthodendrilla sp. J. Nat. Prod. 61: 1374-1378.

Wells RJ (1976). A novel peroxyketal from a sponge. Tetrahedron Letters 17: 2367–8.

Werner EG Müller , Heinz C Schröder, Matthias Wiens, Sanja Perovic-Ottstadt, Renato Batel, Isabel M Müller (2004). Traditional and Modern Biomedical Prospecting: Part II—the Benefits Approaches for a Sustainable Exploitation of Biodiversity (Secondary Metabolites and Biomaterials from Sponges), Advance Access Pub. 1(2): 133–144.

Wright AD, König GM, Angerhofer CK, Greenidge P, Linden A, Desqueyroux-Faúndez R (1996). Antimalarial activity: the search for marine-derived natural products with selective antimalarial activity. J. Nat. Prod. 59: 710-716.

Yousaf M, El Sayed KA, Rao KV, Lim CW, Hu J (1998).-metazoan phylum (Porifera) and those in vertebrates. Transplantation 68: 1215–27.

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