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Review Article

Biological Activity in Coral Reef Organisms: Gorgonians (Octocorallia: Gorgonacea)

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Abstract

A review of bioactivity in gorgonians is presented, with compounds showing different forms of bioactivity categorised and grouped together. These categories include activity against inflammation, tumour growth, cell division, acetylcholine action, cell proliferation, and fouling. Cytotoxicity, neurotoxicity, and toxicity towards micro-organisms, brine shrimp and other invertebrates, fish and other vertebrates are also discussed. Biological activity in gorgonians has been studied since the late 1950s. Since then, significant milestones in gorgonian bioactivity research have been acheived, and these are highlighted, including gorgonian-derived compounds that have shown exceptional pharmaceutical or other commercial potential. To date, the majority of research into gorgonian bioactivity has been concentrated in the Caribbean, and this research has been very fruitful. Although south-east Asian coral reefs boast the world's highest biodiversity, and this diversity includes gorgonians, this promising resource has yet to be tapped effectively. One reason for this lack of interest could be the poorly understood taxonomic status of these animals. This review hopes to generate both basic and applied research interest in this chemically-rich cnidarian order.

Introduction

Literally thousands of novel metabolites have been discovered from marine sources, and it is not possible to review the entire literature comprehensively in one place for every secondary metabolite discovered from marine organisms. Faulkner has, however, been providing very comprehensive reviews since 1984 (1995a, and earlier reviews therein). These reviews only report novel compounds derived from marine organisms, without special regard to novel biological activity. In particular, known compounds with new biological activities are not reported in his reviews. Bioactive crude extracts or partially purified fractions are also omitted in his reviews. To date, there has been no compilation focussing on the various biological activities in compounds from marine organisms.

Gorgonians are prolific producers of a large variety of secondary metabolites, with many of these also showing potent bioactivity. In comparison to other groups of coral reef organisms, gorgonians exhibit significant potential in bioactivity research. In a 1987 review (Munro *et al.*, 1987), 12 out of 153 species with antiviral, antitumour, or cytotoxic compounds were gorgonians. Between 1986 to early 1991, at least 17 new antitumour and cytotoxic

compounds were reported from gorgonians (Schmitz *et al.*, 1993a).

Here, a survey of the literature reporting bioactivity in gorgonians is presented. The purpose of this review is to facilitate research on bioactivity in gorgonian octocorals, especially in the south-east Asian region. The taxonomy of gorgonians in this region is poorly known (Bayer, 1981); only isolated checklists from the Philippines, Indonesia, and Singapore (see Goh and Chou, 1996 for other faunal lists) have been published in the last 30 years. As the taxonomy of south-east Asian gorgonians becomes unravelled, this chemically-prolific group of marine organisms should realise its full potential in bioactivity applications (including pharmaceuticals and agrichemicals), matching the success of natural products from Caribbean gorgonians.

Milestones in Gorgonian Bioactivity Research

In 1958, Burkholder and Burkholder initiated interest in gorgonian (and indeed, of marine organisms in general) bioactivity research with their report of antimicrobial activity in extracts of gorgonians from the Caribbean. This was probably the first published report of biological activity in gorgonian extracts. Eleven years later, Weinheimer and Spraggins (1969) discovered commercially harvestable amounts of prostaglandins in the Caribbean gorgonian *Plexaura homomalla*. At that time, prostaglandins were known to mediate in a diverse array of physiological functions, and research was severely hampered by a lack of supply for the compounds (Faulkner, 1993). Modern interest in marine natural products chemistry has been attributed to this discovery (Faulkner, 1993). In 1986, Fenical's group at the Scripps Institution of Oceanography extracted and structure-elucidated a series of compounds from *Pseudopterogorgia elisabethae* showing significant anti-inflammatory activity (Look *et al.*, 1986). Clinical trials for pseudopterosin E was initiated in 1991, representing the first gorgonian natural product to be subjected to clinical testing (Konig and Wright, 1996). In 1995, it was reported that an extract from *Pseudopterogorgia elisabethae* containing these pseudopterosins had been incorporated in a commercially available cosmetic product (Faulkner, 1995b) - the first commercial application of a natural product from a gorgonian. A derivative of the pseudopterosins, methopterosin is being developed to be used against a range of inflammatory diseases, including arthritis, psoriasis and asthma (Fenical, 1997). In addition to the above, lophotoxin from gorgonians of the genus *Lophogorgia* is used extensively in neurological research (Taylor *et al.*, 1988). Fuscoside, isolated from *Eunicea fusca* is the only marine natural product known to modulate the lipoxygenase pathway of arachidonic acid metabolism in mammalian cells (Jacobson and Jacobs, 1992). It is interesting to note that all the gorgonians mentioned above are from the Caribbean, emphasizing the imbalance in research effort between the Caribbean and elsewhere that we will highlight in this review.

Ecological Perspectives

Gorgonians are sessile marine organisms that have successfully colonised marine habitats from the polar regions to the equator, and from the abyssal ocean tenches to intertidal areas (Alderslade, 1984). In an analysis of the nutritional content of coral reef organisms, Coll (1981) reported that gorgonians were nutritionally more attractive than scleractinian corals to potential predators. Field observations suggest, however, that predation rates by coral reef fish are higher on scleractinians than on gorgonians, although the former are physically better defended by their external calcium carbonate skeletons. The arborescent growth form of gorgonians make their branches especially attractive to settlement by rheophilic fouling organisms.

In general, however, fouling on gorgonians is lower than would be expected. These observations of the lack of predation and fouling on gorgonians lead to the hypothesis that gorgonians are chemically defended. The numerous reports of compounds showing various forms of bioactivity lend support to this idea. Ecologically-relevant research into gorgonian natural products has lagged behind application-based research although the study of gorgonian chemical ecology is growing (see reviews: Sammarco and Coll, 1988; Coll, 1992).

Chronological Review of Gorgonian Bioactivity

The ancient Chinese recognised and used the medicinal properties of *Melitodes* (=*Melithaea*) *squamata* (South China Sea Institute of Oceanology, 1978, in Scheuer, 1988). Red coral (probably the gorgonian *Corallium rubrum* or closely related species) was used as a major ingredient in numerous potions and decoctions by the ancient Greeks and passed on to other early European cultures (Hickson, 1924).

The abbreviations used in the following section are: ED_{50}: dose at which 50% of test organisms show a given response; LD_{50}: dose at which 50% of test organisms are killed; T/C: ratio of test versus control results. Burkholder and Burkholder (1958), who reported the presence of anti-microbial activity in extracts of gorgonians from the Caribbean, were probably the first to publish scientifically on the bioactivity of gorgonian corals. Crassin acetate, isolated from *Pseudoplexaura* spp. four years later (Ciereszko, 1962), was found to be cytotoxic to L1210 cell lines (ED_{50} 0.2 $lgml^{-1}$) and to marginally inhibit (T/C 130 at 50 $lgml^{-1}$) P388 leukemia *in vivo* (Weinheimer and Matson, 1975). Crassin acetate is a major component of several species of *Pseudoplexaura* and has also been found in lesser amounts in *Eunicea calyculata* (Look *et al.*, 1984). Additionally, it has shown inhibitory activity towards cell division in sea urchin eggs (at 16 $lgml^{-1}$; Jacobs *et al.*, 1981). The first discovery of a prostaglandin from a non-mammalian source, and in commercially harvestable amounts was from the gorgonian *Plexaura homomalla* (Weinheimer and Spraggins, 1969). This provided a major impetus for the search for bioactive marine natural products. Two species of *Eunicea*, *E. asperula* and *E. tourneforti*, were the source of the compound asperdiol, which showed significant cytotoxic activity (KB: ED_{50} 24 $lgml^{-1}$; P388: ED_{50} 6 $lgml^{-1}$; L1210: ED_{50} 6 $lgml^{-1}$) (Weinheimer *et al.*, 1977). McEnroe and Fenical (1978) isolated two compounds from the Caribbean gorgonian, *Pseudopterogorgia rigida*, curcuhydroquinone and curcuquinone, which inhibited cell division in fertilised sea urchin eggs at ED_{100} 8 $lgml^{-1}$ and 16 $lgml^{-1}$, respectively. Another species of *Pseudopterogorgia*, *P. acerosa* was the source of pseudopterolide, which also inhibited cell division in fertilised sea urchin eggs (Banduragga *et al.*, 1982). Lophotoxin, isolated from gorgonians of the genus *Lophogorgia*, is a potent neurotoxin (LD_{50} 8 $lgml^{-1}$, IP mice) which also causes ataxia, paralysis and severe respiratory depression (Fenical *et al.*, 1981). While this compound has not seen clinical trials as a potential pharmaceutical drug, its use as a biomedical probe is very important (e.g., Culver *et al.*, 1985; Sorenson *et al.*, 1987; Abramson *et al.*, 1988; Taylor *et al.*, 1988). Two compounds, hippuristanol and 2a-hydroxyhippuristanol, isolated from the Okinawan gorgonian, *Isis hippuris*, were active in the P388 *in vivo* assay (Higa *et al.*, 1981). An ichthyotoxic (at 1 $lgml^{-1}$) sesquiterpenoid, pacifigorgiol, was isolated from the gorgonian *Pacifigorgia* sp. cf. *adamsii* (Izac *et al.*, 1982). Four compounds (butenolides) from *Euplexaura flava* showed significant anti-inflammatory activity at 100 $lgml^{-1}$ (Kikuchi *et al.*, 1982, 1983). An unidentified species of *Euplexaura* was the source of moritoside, which inhibited cell division in fertilised starfish eggs at 1 $lgml^{-1}$ (Fusetani *et al.*, 1985). The pseudopterosins, diterpene

glycosides from *Pseudopterogorgia elisabethae* showed anti-inflammatory activity equivalent to or greater than indomethacin (Look *et al.*, 1986). An extract from this species of gorgonian has now been incorporated in a cosmetic product called Resilience by Estée Lauder (Faulkner, 1995b). Another species of the same genus, *P. kallos*, produced kallolide A, also an anti-inflammatory diterpenoid, which made up 2% of the organic extract (Look *et al.*, 1985). The muricins, isolated from the Pacific gorgonian *Muricea fruticosa* inhibited the fouling marine diatom *Phaeodactylum tricornutum*, but did not show any cytotoxic, antimicrobial or ichthyotoxic effects (Bandurraga and Fenical, 1985). Another potential non-medical application of a compound of gorgonian origin is seen in briarein Y, extracted from the gorgonian *Briareum*, which showed insecticidal activity (LD_{50} < 3mg against the grasshopper). This compound was also found to be toxic to *Salmonella* strains without signs of mutagenicity at 7 $lgml^{-1}$ (Cardellina *et al.*, 1984).

In the past 15 years, research into bioactivity in marine organisms in general, and gorgonians in particular has increased. Out of about 153 species of marine organisms ranging from cyanophytes to tunicates possessing antiviral, antitumour or cytotoxic compounds (Munro *et al.*, 1987), 12 were gorgonians. In the short period between 1986 to early 1991, at least 17 new bioactive compounds were reported to have been isolated from gorgonians (Schmitz *et al.*, 1993a), but this was, in fact, an underestimation as the review only covered antitumour and cytotoxic compounds; several other gorgonian-isolated compounds with potent anti-inflammatory activity (e.g., Groweiss *et al.*, 1988; Shin *et al.*, 1989) were omitted from the review. Three pigment compounds isolated from *Acalycigorgia* sp. showed 'moderate' activity against P388, of which two also showed immunostimulatory activity at 'low concentrations' (Sakemi and Higa, 1987). From the same genus, five norditerpenes with the xenicane skeleton were isolated, and all interfered with cell division in fertilised starfish eggs in the 1-50 $lgml^{-1}$ range (Fusetani *et al.*, 1987a, 1989a; Hokama *et al.*, 1988). A guaiazulene derivative from an *Acalycigorgia* sp. was patented in 1988 by the Harbor Branch Oceanographic Institute; among its described activities are tumour inhibition, cytostatic activity against lung, colon, and mammary carcinomas and showing immunomodulatory and fungicidal characteristics (Derwent Publishing Ltd., 1995). Dimorphosides A and B, from *Anthoplexaura dimorpha*, were reported to inhibit fertilised sea urchin eggs at $IC_{50}6$ $lgml^{-1}$ (Fusetani *et al.*, 1987b). Fusetani's group also isolated astrogorgin, ophirin, and astrogorgiadiol from the gorgonian *Astrogorgia* sp., which inhibited cell division in fertilised starfish eggs at 10, 10, and 6 $lgml^{-1}$, respectively (Fusetani *et al.*, 1989b). Six new diterpenoids, solenolides A-F were isolated from the Pacific gorgonian, *Solenopodium* sp. (Groweiss *et al.*, 1988). Of these, four (solenolides A, D, E and F) were potent anti-inflammatory agents, with activity comparable to that of indomethacin (70% reduction in edema at concentrations in the range of 15 lg for the mouse ear assay). Anti-inflammatory activity was also reported from the junceellolides, new briarane class diterpenoids from the South China Sea gorgonian, *Junceella fragilis* (Shin *et al.*, 1989). Four bipinnatins (a, b, c, d), isolated from *Pseudopterogorgia bipinnata* were active against P388 (IC_{50} 0.9, 3.2, 46.6 and 1.5 $lgml^{-1}$, respectively) (Wright *et al.*, 1989).

Work on bioactive gorgonian secondary metabolites has continued through this decade. Four gorgonian species have been shown to inhibit barnacle settlement (Mary *et al.*, 1991). Brianolide was isolated and structure-elucidated from a *Briareum* sp. collected in Okinawa (Kobayashi *et al.*, 1991) while new briarein diterpenes from *Erythropodium caribaeorum* and *Briareum* sp. were isolated from the Caribbean (Pordesimo *et al.*, 1991). Both research

groups reported anti-inflammatory activity in the new compounds they isolated. Anti-inflammatory activity was also reported for fuscoside, isolated from *Eunicea fusca* in the Caribbean (Jacobson and Jacobs 1992). Inhibitory activity in this compound against edema was comparable to indomethacin in the short term, and significantly more efficacious with longer exposure. Tanaka *et al.* (1992) isolated a new furanosesquiterpene from the gorgonian *Echinogorgia praelonga* that inhibited cell division of fertilised sea urchin eggs. Metabolites with acetylcholine inhibitory activity have recently been isolated from several gorgonians: *Villagorgia rubra* (Espada *et al.*, 1993); *Eunicea* spp. (Eterovic *et al.*, 1993); *Pseudopterogorgia bipinnata* (Bai *et al.*, 1993). In particular, the metabolite isolated from *P. bipinnata*, bipinnatin B, partially blocked nicotine-induced depolarization in the metathoracic ganglion of the cockroach. This suggests its possible development as an insecticide. Pseudoplexaurol and 14-deoxycrassin, two new diterpenoid cytotoxic and antitumour compounds, were isolated from the Caribbean gorgonian, *Pseudoplexaura porosa* (Rodriguez and Martinez, 1993). Rodriguez and Dhasmana (1993) isolated three other bioactive cembranolide diterpenes from *Eunicea succinea*. These cembranolides showed both cytotoxic and anti-tumour properties. Five asbestinin diterpenoids from *Briareum asbestinum* showed significant toxicity when screened against a panel of five human tumour cell lines (Rodriguez and Lobar, 1993). Mild cytotoxicity was reported in briaeolide 4, a newly isolated diterpene from the New Guinean gorgonian, *Solenopodium excavatum* (Schmitz *et al.*, 1993b). Aqueous and ethanol extracts, as well as stress-induced mucus from Caribbean gorgonians were studied by Garcia-Alonso *et al.* (1993): gorgonian mucus was shown to be toxic to crabs, fish, and mice. Extracts exhibited a wide range of activity, including hemolytic, proteolytic, and phospholipase-inhibitory and anti-cholinesterase activities. Kim (1994) found anti-bacterial activity in extracts of eight gorgonians from Panama. Cytotoxicity was reported in palmonine F, isolated from *Eunicella verrucosa* (Ortega *et al.*, 1994). New bioactive secosterols from *Pseudopterogorgia* sp. showed anti-proliferative and anti-inflammatory effects (He *et al.*, 1995). Weak cytotoxicity against HeLa cells was reported from dolabellane diterpenes from *Eunicea laciniata* in the Caribbean (Rodriguez *et al.*, 1995). Five novel diterpenoid compounds isolated from an extract of the Caribbean gorgonian *Eunicea tournefourti*, showed differential activity against mutant and wild-type yeast strains, indicating the presence of potential DNA-interacting agents (Govindan *et al.*, 1995). Goh *et al.* (1995) found antimicrobial and ichthyotoxic properties in extracts of all six gorgonian species from Singapore tested. In the same study, five of the extracts were also toxic in the brine shrimp assay. Goh (1996) continued the work by testing extracts from ten gorgonian species from Singapore, finding activity against gram positive bacteria (nine extracts), gram negative bacteria (4 extracts), and yeast (3 species). Toxicity towards brine shrimp (5 extracts) and goldfish (8 extracts) was also reported. La Barre *et al.* (1996) characterised an elastase inhibitor from a species of *Melithaea* in New Caledonia. Jensen *et al.* (1996) tested 39 gorgonians against 15 marine bacterial strains, and found 30 to inhibit growth in at least one strain.

Range of Bioactivity in Gorgonians and Comments on Collection Locality

Various types of biological activity have been reported for compounds or extracts from gorgonians. Anti-inflammatory activity, cytotoxicity and anti-tumour activity, and inhibition of cell division are among the most common biological activities reported in the literature (Table 1). More than half the number of reports of activity have originated from gorgonians collected in the Caribbean Sea. This is probably a function of the abundance and

Table 1. Known biological activity in gorgonians, including collection locality.

Activity	Compound(s)	Species	Reference; Remarks	Locality
Anti-inflammatory	butenolides	*Euplexaura flava*	Kikuchi *et al.*, 1982, 1983	Western Pacific
	pseudopterosin	*Pseudopterogorgia elisabethae*	Look *et al.*, 1986	Caribbean
	kallolide A	*Pseudopterogorgia kallos*	Look *et al.*, 1985	Caribbean
	solenolides (A, D, E, F)	*Solenopodium* sp.	Groweiss *et al.*, 1988	Western Pacific
	junceellolides	*Junceella fragilis*	Shin *et al.*, 1989	South China Sea
	brianolide	*Briareum* sp.	Kobayashi *et al.*, 1991	Western Pacific
	briarein diterpenes	*Erythropodium caribaeorum*, *Briareum* sp.	Pordesimo *et al.*, 1991	Caribbean
	fuscoside	*Eunicea fusca*	Jacobson & Jacobs, 1992)	Caribbean
	secosterols	*Pseudopterogorgia* sp.	He *et al.*, 1995	Caribbean
Anti-tumour	crassin acetate	*Pseudoplexaura* spp.	Weinheimer & Matson, 1975	Caribbean
	asperdiol	*Eunicea* spp.	Weinheimer *et al.*, 1977	Caribbean
	hippuristanol, 2-a-hydroxyhippuristanol	*Isis hippuris*	Higa *et al.*, 1981	Western Pacific
	pigment compounds	*Acalycigorgia* sp.	Sakemi & Higa, 1987	Western Pacific
	bipinnatins	*Pseudopterogorgia bipinnata*	Wright *et al.*, 1989	Caribbean
	cembranolide diterpenes	*Eunicea succinea*	Rodriguez & Dhasmana, 1993	Caribbean
	asbestinin diterpenoids	*Briareum asbestinum*	Rodriguez & Lobar, 1993	Caribbean
	14-deoxycrassin, pseudoplexaurol	*Pseudoplexaura porosa*	Rodriguez & Martinez, 1993	Caribbean
Cytotoxicity	crassin acetate	*Pseudoplexaura* spp.	Weinheimer & Matson, 1975	Caribbean
	asperdiol	*Eunicea* spp.	Weinheimer *et al.*, 1977	Caribbean
	palmonine F	*Eunicella verrucosa*	Ortega *et al.*, 1994	Caribbean
	cembranolide diterpenes	*Eunicea succinea*	Rodriguez & Dhasmana, 1993	Caribbean
	14-deoxycrassin, pseudoplexaurol	*Pseudoplexaura porosa*	Rodriguez & Martinez, 1993	Caribbean
	briaeolide 4	*Solenopodium excavatum*	Schmitz et al., 1993b	Western Pacific
	dolabellane diterpenes	*Eunicea laciniata*	Rodriguez *et al.*, 1995	Caribbean
Cell division inhibition	crassin acetate	*Pseudoplexaura* spp.	Jacobs *et al.*, 1981	Caribbean
	curcuquinone, curcuhydroquinone	*Pseudopterogorgia rigida*	McEnroe & Fenical, 1978	Caribbean
	pseudopterolides	*Pseudopterogorgia acerosa*	Banduragga *et al.*, 1982	Caribbean
	astrogorgin, ophirin, astrogorgiadiol	*Astrogorgia* sp.	Fusetani *et al.*, 1989	Western Pacific
	furanosesquiterpene	*Echinogorgia praelonga*	Tanaka *et al.*, 1992	Western Pacific
	moritoside	*Euplexaura* sp.	Fusetani *et al.*, 1985	Western Pacific

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Activity	Compound(s)	Species	Reference; Remarks	Locality
	norditerpenes	*Acalycigorgia* sp.	Fusetani *et al.*, 1987, 1989a; Hokama *et al.*, 1988	*Western Pacific*
Acetylcholine inhibition	villagorgins A and B	*Villagorgia rubra*	Espada *et al.*, 1993	Caribbean
	various diterpenoids	*Eunicea* spp.	Eterovic *et al.*, 1993	Caribbean
	bipinnatin B	*Pseudopterogorgia bipinnata*	Bai *et al.*, 1993	Caribbean
Antimicrobial	crude extracts	7 species	Burkholder & Burkholder, 1958	Caribbean
	crude extracts	8 species	Kim, 1994	Caribbean
	crude extracts	6 species	Goh *et al.*, 1995	Singapore
	crude extracts	9 species	Goh, 1996	Singapore
	crude extracts	30 species	Jensen *et al.*, 1996	Caribbean
Neurotoxicity	lophotoxin	*Lophogorgia* sp.	Fenical *et al.*, 1981	Western Pacific
Antiproliferative	secosterols	*Pseudopterogorgia* sp.	He *et al.*, 1995	Caribbean
	pigment compounds	*Acalycigorgia* sp.	Sakemi & Higa, 1987	Western Pacific
Brine shrimp toxicity	crude extracts	6 species	Goh *et al.*, 1995	Singapore
	crude extracts	8 species	Goh, 1996	Singapore
Ichthyotoxicity	pacifigorgiol	*Pacifigorgia cf. adamsii*	Izac et al., 1982	Western Pacific
	crude extracts	6 species	Goh *et al.*, 1995	Singapore
	crude extracts	8 species	Goh, 1996	Singapore
Fish, crab, mice toxicity	aqueous extract, ethanol extract, stress-induced mucus	8 species	Garcia-Alonso *et al.*, 1993	Caribbean
Antifouling	muricins	*Muricea fruticosa*	Banduragga & Fenical, 1985; diatom toxicity	Eastern Pacific
	crude extracts	4 species	Mary *et al.*, 1991; barnacle inhibition	Indian Ocean
Insecticidal	briarein Y	*Briareum* sp.	Cardellina et al., 1984	Caribbean
	bipinnatin B	*Pseudopterogorgia bipinnata*	Bai *et al.*, 1993	Caribbean

shallow-water occurrence of this fauna in the Caribbean, contributing to the ease of collections. Another factor is the mature state of gorgonian systematics and taxonomy in that area. The remaining reports are mainly from the Pacific (Eastern and Western). Until recently, the south-east Asian region was largely unrepresented in the literature. The poor state of gorgonian taxonomy in this region no doubt contributes to the dearth of research of this type here. At the same time, this speaks of the tremendous potential for bioactivity research on gorgonians from this region as more workers focus on this chemically-rich order of marine organisms.

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References

Abramson, S.N., Culver, P., Kline, T., Li, Y., Guest, P., Gutman, L. and Taylor, P. (1988) Lophotoxin and related coral toxins covalently label the alpha-subunit of the nicotinic acetylcholine receptor. *J. Biol. Chem.* 263: 18568-18573.

Alderslade, P.N. (1984) Subclass Alcyonaria. In *A coral reef handbook, 2nd edition*, P. Mather and I. Bennet (editors), pages 45-48. The Australian Coral Reef Society.

Bai, D., Abramson, S.N. and Sattelle, D.B. (1993) Actions of a coral toxin analogue (bipinnatin B) on an insect nicotinic acetylcholine receptor. *Arch. Insect. Biochem. Physiol.* 23: 155-159.

Bandurraga, M.M. and Fenical, W. (1985) Isolation of the muricins. Evidence of a chemical adaptation against fouling in the marine octocoral *Muricea fruticosa* (Gorgonacea). *Tetrahedron* 41: 1057-1065.

Bandurraga, M.M., Fenical, W., Donovon, S.F. and Clardy, J. (1982) Pseudopterolide, an irregular diterpenoid with unusual cytotoxic properties from the caribbean sea whip *Pseudopterogorgia acerosa* (Pallas) (Gorgonacea). *J. Am. Chem. Soc.* 104: 6463- 6465.

Bayer, F.M. (1981) Status of knowledge of octocorals of world seas. *Seminarios de Biologia Marinha*, pages 3-11. Academia Brasiliera de Ciencias, Rio de Janiero.

Burkholder, P.R. and Burkholder, L.M. (1958) Antimicrobial activity of horny corals. *Science (Washington, D.C.)* 127: 1174.

Cardellina, J.H., James, T.R., Chen, M.H.M. and Clardy, J. (1984) Structure of brianthein W from the soft coral *Briareum polyanthus*. *J. Am. Chem. Soc.* 49: 3398-3399.

Cieresko, L.S. (1962) Chemistry of coelenterates III. Occurrence of antimicrobial terpenoid compounds in the zooxanthellae of alcyonarians. *Trans. N.Y. Acad. Sci.* 24: 502.

Coll, J.C. (1981) Soft coral research at James Cook University of North Queensland. *Proc. 4th Asian Symp. Med. Plants and Spices. UNESCO Spec. Publ., Bangkok,* pp. 197-204.

Coll, J.C. (1992) The chemistry and chemical ecology of octocorals (Coelenterata, Anthozoa, Octocorallia). *Chem. Rev.* 92: 613-631.

Culver, P., Burch, M., Potenza, C., Wasserman, L., Fenical, W. and Taylor, P. (1985) Structure-activity relationships for the irreversible blockade of nicotinic receptor agonist sites by lophotoxin and congeneric diterpene lactones. *Mol. Pharmacol.* 28: 436-444.

Derwent Publishing Ltd. (1995) Derwent Biotechnology Abstracts Database: July 1982-June 1995, London, England.

Espada, A., Jimenez, C., Debitus, C. and Rodriguez, R. (1993) Villagorgin A and B: new type of indole alkaloids with acetylcholine antagonist activity from the gorgonian *Villagorgia rubra*. *Tetrahedron Lett.* 34: 7773-7776.

Eterovic, V.A., Hann, R.M., Ferchmin, P.A., Rodriguez, A.D., Li, L., Lee, Y.H. and McNamee, M.G. (1993) Diterpenoids from Caribbean gorgonians act as noncompetitive inhibitors of the nicotinic acetylcholine receptor. *Cellular and Mol. NeuroBiol.* 13: 99-110.

Faulkner, D.J. (1993) Academic chemistry and the discovery of bioactive marine natural products. In *Marine Biotechnology, Vol. 1: Pharmaceutical and Bioactive Natural Products,* D.H. Attaway and O.R. Zaborsky (editors), pages 459-474. Plenum Press, New York.

Faulkner, D.J. (1995a) Marine natural products. *Nat. Prod. Rep.* 12: 223-269.

Faulkner, D.J. (1995b) Chemical riches from the oceans. *Chem. in Britain,* Sep. 1995: 680-684.

Fenical, W. (1997) New pharmaceuticals

from marine organisms. *Trends in Biotech.*15: 339-341.

Fenical, W., Okuda, R.K., Bandurraga, M.M., Culver, P. and Jacobs, R.S. (1981) Lophotoxin: a novel neuromuscular toxin from the Pacific sea whips of the genus *Lophogorgia. Science* 212: 1512-1514.

Fusetani, N., Yasukawa, K., M., Matsunaga, S. and Hashimoto, K. (1985) Bioactive marine metabolites. XII. Moritoside, an inhibitor of the development of starfish embryo, from the gorgonian *Euplexaura* sp. *Tetrahedron Lett.* 26: 6449-6452.

Fusetani, N., Asano, M., Matsunaga, S. and Hashimoto, K. (1987a) Acalycixeniolides, novel norditerpenes which inhibit cell division of fertilised starfish eggs, from the gorgonian *Acalycigorgia inermis. Tetrahedron Lett.* 28: 5837-5840.

Fusetani, N., Yasukawa, K., M., Matsunaga, S. and Hashimoto, K. (1987b) Dimorphosides A and B, novel steroid glycosides from the gorgonian *Anthoplexaura dimorpha. Tetrahedron Lett.* 28: 1187-1190.

Fusetani, N., Asano, M., Matsunaga, S. and Hashimoto, K. (1989a) Bioactive marine metabolites. Acalycixeniolides, novel norditerpenes with allene functionality from two gorgonians of the genus *Acalycigorgia. Tetrahedron* 45: 1647-1652.

Fusetani, N., Nagata, H., Hirota, H. and Tsuyuki, T. (1989b) Astrogorgiadiol and astrogorgin, inhibitors of cell division in fertilised starfish eggs, from a gorgonian *Astrogorgia* sp. *Tetrahedron Lett.* 30: 7079-7082.

Garcia-Alonso, I., Martinez, J.R., Aneiros, A., Acosta, A., Llanio, M., Diaz, M., Concepcion, A.R., Cowley, S., Morales, A., Perez, M., Gonzalez, O. and Llorente, S. (1993) Biological activity of secretions and extracts of gorgonians from Cuban waters. *J. Nat. Toxins* 2: 27-39.

Goh, N.K.C. (1996) *Studies on the biology and bioactivity of Singapore gorgonaceans (Sub-class Octocorallia).* Ph.D. thesis, National University of Singapore, 227 pp.

Goh, N.K.C. and Chou, L.M. (1996) An annotated checklist of the gorgonians (Anthozoa: Octocorallia) of Singapore, with a discussion of gorgonian diversity in the Indo-West Pacific. *Raff. Bull. Zool.* 44: 435-459.

Goh, N.K.C., Sim, T.S. and Chou, L.M. (1995) Bioactivity of gorgonians (sub-class Octocorallia) in Singapore: preliminary studies. *Mar. Res.* 4: 33-46.

Govindan, M., Govindan, G.N. and Kingston, D.G.I. (1995) Mechanism-based antitumor screening of Caribbean marine organisms: Isolation and structure determination of novel diterpenoids from the gorgonian *Eunicea tournefourti. J. Nat. Prod.* 58: 1174-1184.

Groweiss, A., Look, S.A. and Fenical, W. (1988). Solenolides, new anti-inflammatory and antiviral diterpenoids from a marine octocoral of the genus *Solenopodium. J. Org. Chem.* 53: 2401-2406.

He, H., Kulanthaivel, P., Baker, B.J., Kalter, K., Darges, J. Cofield, D., Wolff, L. and Adams, L. (1995) New antiproliferative and anti-inflammatory 9, 11-secosterols from the gorgonian *Pseudopterogorgia* sp. *Tetrahedron* 51: 51-58.

Hickson, S.J. (1924) *An introduction to the study of recent corals* (The early trade in black and red coral, chapter XII), pages 231-250. Publ. Univ. Manchester, Biol. Ser. No. IV.

Higa, T., Tanaka, J., Tsukitani, Y. and Kikuchi, H. (1981) Hippuristanols, cytotoxic polyoxygenated steroids from the gorgonian Isis hippuris. *Chem. Lett.* (1981): 1647-1650.

Hokama, S., Tanaka, J., Higa, T., Fusetani, N., Asano, M., Matsunaga, S. and Hashimoto, J. (1988) Bioactive marine metabolites. Ginamellene, a new norditerpene with allene functionality from four gorgonians of the genus *Acalycigorgia. Chem. Lett.* 1988: 855.

Izac, R.R., Poet, S.E., Fenical, W., Van Engen, D. and Clardy, J. (1982) The structure of

pacifigorgiol, an ichthyotoxic sesquiterpenoid from the Pacific gorgonian coral *Pacifigorgia* cf. *adamsii*. *Tetrahedron Lett.* 23: 3743-3746.

Jacobson, P.B. and Jacobs, R.S. (1992) Fuscoside: An anti-inflammatory marine natural product which selectively inhibits 5-lipoxygenase. Part I: Physiological and biochemical studies in murine inflammatory models. *J. Pharmacog. Exp. Ther.* 262: 866-873.

Jacobs, R.S., White, S. and Wilson, L. (1981) Selective compounds derived from marine organisms: effects on cell division in fertilized sea urchin eggs. *Fed. Proc.* 40: 26-29.

Jensen, P.R., Harvell, C.D., Wirtz, K. and Fenical, W. (1996) Antimicrobial activity of extracts of Caribbean gorgonian corals. *Mar. Biol.* 125: 411-419.

Kikuchi, H., Tsukitani, Y., Nakanishi, H., Shimizu, S., Saitoh, S., Iguchi, K. and Yamada, Y. (1982) New butenolides from the gorgonian *Euplexaura flava* (Nutting). *Chem. Lett.* 233-236.

Kikuchi, H., Tsukitani, Y., Nakanishi, H., Shimizu, S., Saitoh, S., Iguchi, K. and Yamada, Y. (1983) Studies on marine natural products, VIII. New butenolides from the gorgonian *Euplexaura flava* (Nutting). *Chem Pharm. Bull.* 31: 1172-1176.

Kim, K. (1994) Antimicrobial activity in gorgonian corals (Coelenterata, Octocorallia). *Coral Reefs* 13: 75-80.

Kobayashi, J., Cheng, J.F., Nakamura, H., Ohizumi, Y., Tomotake, Y., Matsuzaki, T., Grace, K.J.S., Jacobs, R.S., Kato, Y., Brinen, L.S. and Clardy, J. (1991) Structure and stereochemistry of brianolide, a new anti-inflammatory diterpenoid from the Okinawan gorgonian *Briareum sp. Experientia (Basel)* 47: 501-502.

Konig, G.M. and Wright, A.D. (1996) Marine natural products: Current directions and future potential. *Planta Medica* 62: 193-211.

La Barre, S., Longeon, A., Bartelemy, M., Guyot, M., Le, R.J.P. and Bargibant, G. (1996) Characterisation of a novel elastase inhibitor from a fan coral. *Comptes Rendus de l'Academie des Sciences Serie III Sciences de la Vie* 319: 365-370.

Look, S.A., Fenical, W., Zheng, Q. and Clardy, J. (1984) Calyculones, new cubitane diterpenoids from the Caribbean octocoral *Eunicea calyculata*. *J. Org. Chem.* 49: 1417-1423.

Look, S.A., Burch, M.T., Fenical, W., Qi-Tai, Z. and Clardy, J. (1985) Kallolide A, a new anti-inflammatory diterpenoid, and related lactones from the Caribbean octocoral *Pseudopterogorgia kallos*. *J. Org. Chem.* 50: 5741-5746.

Look, S.A., Fenical, W., Jacobs, R.S. and Clardy, J. (1986) The pseudopterosins: Anti-inflammatory and analgesic natural products from the sea whip *Pseudopterogorgia elisabethae*. *Proc. Nat. Acad. Sci. USA* 83: 6238-6240.

Mary, S.R., Mary, S.A., Rittschof, D., Sarojini, R. and Nagabhushanam, R. (1991) Compounds from octocorals that inhibit barnacle settlement: isolation and biological potency. In *Bioactive compounds from marine organisms, with emphasis on the Indian Ocean*, M-F Thomson, R. Sarojini and R. Nagabhushanam (editors), pages 331-339.

McEnroe, F.J. and Fenical, W. (1978) Structures and synthesis of some new antibacterial sesquiterpenoids from the gorgonian *Pseudopterogorgia rigida*. *Tetrahedron* 34: 1661-1664.

Munro, M.H.G., Luibrand, R.T. and Blunt, J.W. (1987) The search for antiviral and anticancer compounds from marine organisms. In *Bioorganic marine chemistry, Vol. 1*, P.J. Scheuer (editor), pages 93-176. Springer-Verlag, Berlin-Heidelberg.

Ortega, M.J., Zubia, E. and Salva, J. (1994) Structure and absolute configuration of palmonine F, a new eunicellin-based diterpene from the gorgonian *Eunicella verrucosa*. *J. Nat. Prod.* 57: 1584-1586.

Pordesimo, E.O., Schmitz, F.L., Ciereszko,

L.S., Hossain, M.B. and Van-Der-Helm, D. (1991) New briarein diterpenes from the Caribbean gorgonians *Erythropodium caribaeorum* and *Briareum sp. J. Org. Chem.* 56: 2344-2357.

Rodriguez, A.D. and Dhasmana, H. (1993) Further bioactive cembranolide diterpenes from the gorgonian *Eunicea succinea. J. Nat. Prod.* 56: 564-570.

Rodriguez, A.D. and Lobar, O.M. (1993) Structures and bioactivities of new asbestinin diterpenoids from the Caribbean gorgonian octocoral *Briareum asbestinum. Tetrahedron* 49: 319-328.

Rodriguez, A.D. and Martinez, N. (1993) Marine antitumour agents: 14-deoxycrassin and pseudoplexaurol, new cembranolide diterpenes from the Caribbean gorgonian *Pseudoplexaura porosa. Experientia (Basel)* 49: 179-181.

Rodriguez, A.D., Gonzalez, E. and Gonzalez, C. (1995) Additional dolabellane diterpenes from the Caribbean gorgonian octocoral *Eunicea laciniata. J. Nat. Prod.* 58: 226-232.

Sakemi, S. and Higa, T. (1987) 2,3 Dihydrolinderazulene, a new bioactive azulene pigment from the gorgonian *Acalycigorgia* sp. *Experimentia* 43: 624-625.

Sammarco, P.W. and Coll, J.C. (1988) The chemical ecology of alcyonarian corals (Coelenterata: Octocorallia). In *Bioorganic marine chemistry, Vol. 2*, P.J. Scheuer (editor), pages 87-116. Springer-Verlag.

Scheuer, P.J. (1988) Ethno-natural historical leads. In *Biomedical importance of marine organisms*, D.G. Fautin (editor), pages 37-40. Memoirs of the California Academy of Sciences, Number 13.

Schmitz, F.J., Bowden, B.F. and Toth, S.I. (1993a) Antitumor and cytotoxic compounds from marine organisms. In *Marine Biotechnology, Volume 1: Pharmaceutical and bioactive natural products*, D.H. Attaway and O.R. Zaborsky (editors), pages 197-308. Plenum Press, New York.

Schmitz, F.J., Schulz, M.M., Siripitayananon, J., Hossain, M.B. and van der Helm, D. (1993b) New diterpenes from the gorgonian *Solenopodium excavatum. J. Nat. Prod.* 56: 1339-1349.

Shin, J., Park, M. and Fenical, W. (1989) The junceellolides, new anti-inflammatory diterpenoids of the briarane class from the Chinese gorgonian *Junceella fragilis. Tetrahedron* 45: 1633-1638.

Sorenson, E.M., Culver, P. and Chiapinelli, V.A. (1987) Lophotoxin: Selective blockade of nicotinic transmission in autonomic ganglia by a coral neurotoxin. *Neuroscience* 20: 875-884.

Tanaka, J., Miki. H. and Higa, T. (1992) Echinofuran, a new furanosesquiterpene from the gorgonian *Echinogorgia praelonga. J. Nat. Prod.* 55: 1522-1524.

Taylor, P., Culver, P., Abramson, S., Wasserman, L., Kline, T. and Fenical, W. (1988) Use of selective toxins to examine acetylcholine receptor structure. In *Biomedical importance of marine organisms*, D.G. Fautin (eitor.), pages 109-114. Memoirs of the California Academy of Sciences, Number 13.

Weinheimer, A.J. and Matson, J.A. (1975) Crassin acetate, the principal antineoplastic agent in four gorgonians of the *Pseudoplexaura* genus. *Llyodia* 38: 378-382.

Weinheimer, A.J. and Spraggins, R.L. (1969) The occurrence of new prostaglandin derivatives (15-*epi*-PGA_2 and its acetate, methyl ester) in the gorgonian *Plexaura homomalla. Tetrahedron Lett.* 1969: 5185-5188.

Weinheimer, A.J., Matson, J.A., van der Helm, D. and Poiling, M. (1977) Marine anticancer agents: asperdiol, a cembranoid from the gorgonians *Eunicea asperula* and *E. tournefourti. Tetrahedron Lett.* 1295.-1298.

Wright, A.E., Burres, N.S. and Schulte, G.K. (1989) Cytotoxic cembranoids from the gorgonian *Pseudopterogorgia bipinnata. Tetrahedron Lett.* 30: 3491-3494.