Natural Marine Anti-inflammatory Products

María José Abad*, Luis Miguel Bedoya and Paulina Bermejo

Department of Pharmacology, Faculty of Pharmacy, University Complutense, Ciudad Universitaria s/n, 28040, Madrid, Spain

Abstract: The marine environment has been shown to be the source of a great diversity of chemical structures with promising biological activities. The isolation, biological evaluation, chemical properties and synthetic elaborations of the products of marine organisms and microorganisms have attracted the attention of organic chemists, medicinal chemists, biologists and pharmacists. Marine organisms and microorganisms have provided a large proportion of the natural anti-inflammatory products over the last years. Marine organisms include green algae, brown algae, red algae, sponges, coelenterates, bryozoans, molluscs, tunicates, echinoderms, miscellaneous marine organisms and marine microorganisms and phytoplankton. This review describes current progress in the development of a selection of new anti-inflammatory agents from marine sources. The chemistry and biological evaluation are discussed.

INTRODUCTION

Natural products are the most consistently successful source of drug leads. Despite this, their use in drug discovery has fallen out of favour. Natural products continue to provide greater structural diversity than standard combinatorial chemistry and therefore offer major opportunities for finding novel structures that are active against a wide range of assay targets. As less than 10% of the world's biodiversity has been tested for biological activity, many more useful natural lead compounds are awaiting discovery [1, 2]. The challenge is how to access this natural chemical diversity.

Marine organisms represent an enormous, essentially unexploited, resource of natural products. Natural marine products constitute a field of scientific endeavour that in recent years has grown considerably. The isolation, biological evaluation, chemical properties and synthetic elaborations of the products of marine organisms and microorganisms have attracted the attention of organic chemists, medicinal chemists, biologists and pharmacists. The enormous potential of the sea as a source of energy, food and chemicals has led to its being the subject of intense research. The results of this search have been reported in numerous reviews [3-8]. The marine environment has been shown to be the source of a great diversity of chemical structures with promising biological activities. After the identification of a potential substance, several hurdles have to be overcome before a marine candidate can enter the clinic. However, a growing number of these compounds are entering clinical trials and thus the impact of this field on the biomedical industry is increasing. Recent patents involving natural marine products have focused on the discovery of anti-inflammatory agents [9-12].

During the past few decades, intensive collaborative research in the fields of chronic and acute inflammatory diseases has resulted in a better understanding of the pathophysiology and diagnosis of these diseases. Modern therapeutic approaches are still not satisfactory and shock, sepsis and organ failure remain the great challenges in intensive care medicine. However, the treatment of inflammatory diseases also represents an unresolved problem. Many factors contribute to the complex course of inflammatory reactions. Microbiological, immunological and toxic agents can initiate the inflammatory response by activating a variety of humoral and cellular mediators. Progression of inflammatory processes correlates with the release of these cell-derived mediators from the local site of inflammation. These mediators include prostaglandins (PGs), leukotrienes (LTs), nitric oxide (NO), tumour necrosis factor-α (TNF-α) and cytokines of the interleukin (IL) families. In the early phase of inflammation, excessive amounts of lipid-mediators are released and play a crucial role in the pathogenesis of organ dysfunction. Arachidonic acid (AA), the mother substance of the pro-inflammatory eicosanoids, is released from membrane phospholipids in the course of inflammatory activation and is metabolised to PGs and LTs. Various strategies have been evaluated to control the excessive production of lipid mediators on different levels of biochemical pathways, such as inhibition of phospholipase A_2 (PLA_2), the trigger enzyme for release of AA, blockage of cyclooxygenase (COX) and lipoxygenase (LOX) pathways, and the development of receptor antagonists against platelet activating factor (PAF) and LTs. Other key enzymes that mediate inflammatory processes also make them attractive drug targets include COX-2, inducible nitric oxide synthase (iNOS) and protein kinase C (PKC), a ubiquitous enzyme with a key role in cellular function. The cytokines of the IL families act on host cells and exert their action by activating their signal transduction pathways leading to specific target gene activation. Pharmacological control of IL production may be a key therapeutic strategy for modulating inflammatory and immunological diseases dominated by this type of cytokine responses. Additionally, since the identification of TNF-α as a major pro-inflammatory cytokine which regulates inflammation, several protein-based TNF-α inhibitors have been approved for clinical use in various inflammatory diseases. The nuclear factor κB (NF-κB) is a dimeric transcription factor

*Address correspondence to this author at the Department of Pharmacology, Faculty of Pharmacy, University Complutense, Ciudad Universitaria s/n, 28040, Madrid, Spain; E-mail: mjabad@farm.ucm.es

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that activates the expression of many genes involved in pathological conditions. The inappropriate activation of NF-κB in diseases such as rheumatoid arthritis and systemic inflammatory response has been attributed to TNF-α and other members of its superfamily. Furthermore, the participation of reactive oxygen species (ROS) in the mechanism of many chronic and acute inflammatory diseases has focused the attention of researchers on the potential protective functions of antioxidants.

Marine organisms and microorganisms have provided a large proportion of the anti-inflammatory and natural antioxidants products over the last years. Marine organisms include green algae, brown algae, red algae, sponges, coelenterates, bryozoans, molluscs, tunicates, echinoderms, miscellaneous marine organisms and marine microorganisms and phytoplankton. This review describes current progress in the development of a selection of new anti-inflammatory agents from marine sources. The chemistry and biological evaluation are discussed.

CRUDE EXTRACTS

In order to develop new drugs from underutilised marine sources, the chemistry and medicinal chemistry of marine organisms and microorganisms were investigated. Their extracts were screened for anti-inflammatory activity using a variety of pharmacological assays.

Spirulina (Arthospira), a filamentous unicellular alga, is a cyanobacterium used in certain countries as foods for human and animal consumption; is one of the most extensively studied from the chemical, pharmacological and toxicological points of view [13]. It is also used to derive additives for pharmaceuticals and foods. This alga is a rich source of proteins, vitamins, amino acids, minerals and other nutrients. Its main use is therefore as a food supplement. Over the last few years, however, it has been found to have many additional pharmacological properties, including anti-inflammatory activity. The anti-inflammatory effect of *Spirulina* was studied in zymosan-induced arthritis in mice [14]. *Spirulina* significantly reduced the levels of β-glucuronidase that had been increased by zymosan. Histopathological and ultrastructural studies showed inhibition of the inflammatory reaction. *Spirulina*, at a dose of 1500 mg/Kg orally, also exhibited significant *in vivo* antioxidant and lipid peroxidation inhibitory activities in arthritic rats [15]. Different *Spirulina* preparations influence the immune system via increased phagocytic activity of macrophages, stimulating the production of antibodies and cytokines, increased accumulation of natural killer (NK) cells into tissues and activation and mobilisation of T and B cells [16]. A pharmacological study of hydrosoluble and liposoluble extracts of other marine microalgae *Chlorella stigmatophora* and *Phaeodactylum tricornutum* indicated that hydrosoluble components of both species show significant anti-inflammatory and free radical scavenging activity [17]. These activities were not detected in the liposoluble fractions.

Reports for the potential medicinal value of seaweeds from all over the world have also been found in the literature. Eleven macroalgae from South Africa were collected from the Kwazulu-Natal coast and nineteen from the cooler Western Cape coast. Ethanolic and aqueous extracts were made and tested for biological activity in the COX-1 anti-inflammatory assay [18]. The ethanolic extracts were active in the COX-1 anti-inflammatory assay for almost all of the species tested. To discover sources of antioxidant activity in marine algae, extracts from seventeen kinds of seaweed were screened for their inhibitory effect on ROS generation in kidney homogenates using 2',7'-dichlorofluorescin diacetate [19]. ROS inhibition was seen in three species: *Ulva pertusa*, *Symphyocladia latiuscula* and *Ecklonia stolonifera*. In another *Ecklonia* species, *Ecklonia cava*, Heo and coworkers [20] investigated its potential antioxidant activity by 1,1-diphenyl-2-picrylhydrazil (DPPH), hydroxyl and alkyl radical scavenging. These results indicate that *Ecklonia cava* might be a valuable source of natural antioxidant. More recently, Kim and coworkers [21] demonstrated that the ethanolic extract of this brown alga significantly reduced the concentrations of TNF-α and cytokines, including IL-4 and IL-5, in a murine asthma model.

Aqueous and ethanolic extracts were also prepared from three brown algae Phaeophyceae, *Scytosiphon lomentaria*, *Papenfusiella kuramo* and *Nemacystus decipiens*, and one Rhodophyceae, *Porphyria* spp. Kuda and coworkers [22] studied their antioxidant properties, including suppression of haemoglobin-induced linoleic acid peroxidation, reducing power, ferrous ion chelating, DPPH-radical scavenging and scavenging of superoxide anion radical-generated non-enzymatic system. Aqueous extracts showed strong antioxidant activities, while the antioxidant activity of ethanolic extracts was not detected or was very low compared to that of aqueous extracts. The free radical scavenging activity of water soluble extracts from *Sargassum thunbergii* and *Sargassum horneri*, brown marine algae, was evaluated on hydroxyl, DPPH and alkyl radicals [23, 24]. The scavenging results were higher for hydroxyl and alkyl radicals, and lower for DPPH radical. Examples of other anti-inflammatory crude extracts of algae origin also included extracts from a brown seaweed *Scytosiphon lomentaria* which exhibited strong scavenging activity [25], and a butanol soluble extract from the edible red alga *Palmaria palmata* [26]. Another marine red alga with antioxidant activity is *Neorhodomela aculeata*, which inhibited ROS generation and iNOS in the murine hippocampal HT22 cell line [27].

Reports that marine invertebrates represent new marine resources for the isolation of novel agents which are active on inflammatory conditions have also been found in the literature. Herencia and coworkers [28] studied the effects of dichloromethane and methanol extracts from some Mediterranean marine invertebrates on carrageenan-induced paw edema in mice. The dichloromethane extract of *Coscinasterias tenuispina* and the methanol extract of *Holothuria tubulosa* inhibited the edema in a dose-dependent manner. Both extracts partially decreased elastase activity and PGE_2 levels measured in homogenates from inflamed paws, without affecting the levels of this prostanoid present in stomach homogenates. Within the framework of the European MAST III Project, extracts of different polarity from sponges, ascidians and cnidarians have been screened for immunomodulating activities [29]. It was demonstrated that endotoxin-free sam-

ples of marine origin possess effects on certain components of the immune system.

As a result of all these investigations, bioassay-directed separation of active extracts identified many structurally diverse compounds as future leads. Anti-inflammatory compounds found in the marine environment include terpenes and steroids, alkaloids, peptides and proteins, polysaccharides and others.

TERPENOIDS

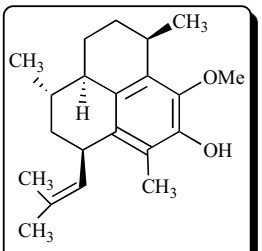
Terpenoids are widely distributed in nature and are found in abundance in higher plants. Marine organisms are a prolific source of unusual terpenoids. Natural terpenoids have dominated the subject of chemical ecology, and terpenoids have been assigned roles as phytoalexins, insect antifeedants and repellents, pollination attractants, defence agents against herbivores, pheromones, allelochemicals, plant hormones and signal molecules. Terpenoid molecules have been implicated in almost every possible interaction between plant and animal, plant and plant, or plant and microorganism.

During the formation of terpenoids, the isoprene units are usually linked in a head-to-tail manner, and the number of units incorporated into a particular unsaturated hydrocarbon terpenoid serves as a basis for the classification of these compounds. Monoterpenoids are composed of two units and have the molecular formula $C_{10}H_{16}$; sesquiterpenoids $C_{15}H_{24}$ contain three isoprene units; diterpenoids $C_{20}H_{32}$ have four isoprene units; sesterterpenoids $C_{25}H_{40}$ have five isoprene units; triterpenoids $C_{30}H_{48}$ are composed of six isoprene units; and tetraterpenoids or carotenoids $C_{40}H_{60}$ have eight units.

Although the study of terrestrial terpenes dates back to the last century, marine terpenes were not discovered until 1955. Reports on the anti-inflammatory activity of marine diterpenes have been found in the literature and are presented below. Chemical investigations have revealed soft corals and gorgonians as a rich source of secondary metabolites, mainly diterpenes. Some of these investigations focused on the ecological function of soft coral terpenoids and showed them to play an important role in the interaction between marine organisms, or indicated that terpenoid content was useful in the taxonomic identification of soft corals. Other studies reported significant biological activities for several diterpenoids, including anti-inflammatory properties.

Pseudopterosin E (**1**), a C-10 linked fucose diterpene glycoside, and pseudopterosin A, a C-9 xylose glycoside isolated from the marine gorgonian *Pseudopterogorgia elisabethae* were both effective in reducing phorbol myristate acetate (PMA)-induced mouse ear edema when administered topically [30]. *In vitro*, the pseudopterosins inhibited PGE_2 and LTC_4 production in zymosan-stimulated murine peritoneal macrophages. These data suggest that the pseudopterosins may mediate their anti-inflammatory effects by inhibiting eicosanoid release from inflammatory cells. A semisynthetic derivative of pseudopterosin A, OAS-1000, has also been shown to have topical anti-inflammatory activity [31].

From the South African soft coral *Eleutherobia aurea*, three diterpenes, zahavin A, 9-deacetoxy-14,15-deepoxyxeniculin and 7,8-epoxy-zahavin A, were isolated [32]. These three diterpenoids inhibit superoxide production in rabbit-cell neutrophils. Three new diterpenes hexose-glycosides, calyculaglycosides A-C, were isolated from the Caribbean gorgonian *Eunicea* spp. [33]. Calyculaglycosides are rare diterpene glycosides possessing dilophol aglycones related in biosynthetic origin to the elemene-type glycoside class. Calyculaglycoside B inhibits the synthesis of both PGE_2 and LTC_4, suggesting that it is a nonselective inhibitor of the 5-LOX and COX pathways.



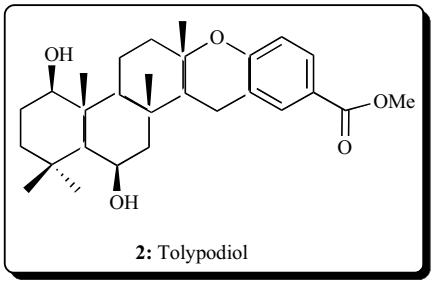
1: Pseudopterosin E

Seo and coworkers [34] isolated five diterpenoids of the cladiellin class from the gorgonian *Muricella* spp. These compounds exhibit moderate inhibitory activity against PLA_2. Xenicane diterpenes with anti-inflammatory activity were also isolated from the soft coral family Nephtheiidae. Diterpenoids of the xenicane and related carbon skeleton classes have been frequently encountered in coelenterates of the orders Gorgonacea (gorgonians) and Alcyonacea (soft corals). The endemic South African soft coral *Capnella thyrsoidea* yielded four xenicane diterpenes, the tsitsixenicins A-D, some of which inhibit superoxide production in both rabbit and human cell neutrophils [35]. Two norditerpenes, norcembranolide and sinuleptolide isolated from the Okinawan soft coral *Sinularia* spp., inhibited TNF-α production in lipopolysaccharide (LPS)-stimulated murine macrophage-like cells RAW 2647 [36]. These compounds also exhibited an inhibitory effect on NO production. Radhika and coworkers [37] investigated the *in vivo* anti-inflammatory activity of the cembrane diterpene named lobohedleolide, isolated from the marine soft coral *Sinularia crassa*. The anti-inflammatory activity was evaluated using the carrageenan-induced rat hindpaw edema model for acute inflammation, and the cotton pellet granuloma model for chronic inflammation. The cembranoid diterpene produced the maximum effect at a dose of 10 mg/Kg, and this is comparable to that of the reference compound, indomethacin. The observed anti-inflammatory activity is almost identical on both types of experimental inflammation.

Other marine organisms and microorganisms such as algae, fungus, sponges and cyanobacteria, also yielded bioactive anti-inflammatory diterpenes. Okai and Higashi [38] investigated the anti-inflammatory effects of pheophytin, a diterpene compound identified from an edible green alga *Enteromorpha prolifera*. Pheophytin suppressed the production of superoxide anion in mouse macrophages induced by PMA using the cytochrome C reduction method. This compound also exhibited a significant suppression of PMA-induced inflammatory reaction such as edema formation in BALB/c mouse ear. Sargachromanols A-P are new meroter-

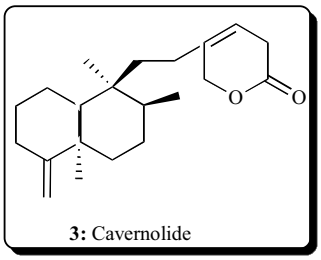
penoids of the chromone class isolated from the brown alga *Sargassum siliquastrum* collected from Jaejn Islands, Korea [39]. The new compounds exhibited significant antioxidant activity in the DPPH assay. Phomactins, natural diterpenes isolated from the culture broth of marine fungus *Phoma* spp., were found to be active as PAF antagonists [40, 41]. PAF, identified as 1-*O*-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcoline, exhibits potent pro-inflammatory properties. Phomactins inhibited the binding of PAF to its receptors and PAF-induced platelet aggregation.

Prinsep and coworkers [42] isolated a new diterpenoid, tolypodiol (**2**), from the cyanobacterium *Tolypothrix nodosa*. Tolypodiol and its monoacetate derivative show potent anti-inflammatory activity in the mouse ear edema assay. Other



2: Tolypodiol

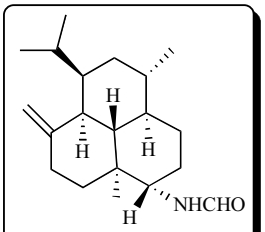
anti-inflammatory marine diterpenes included epitaondiol, ircinin and cavernolide (**3**). The diterpene epitaondiol isolated from the marine alga *Stypopodium flabelliforme* exhibited a potent topical anti-inflammatory activity related to inhibition of leukocyte accumulation [43]. This compound decreased the release of eicosanoids with a higher potency on the COX pathway, and inhibited human recombinant synovial phospholipase. From another marine brown alga, *Stypopodium zonale*, three anti-inflammatory diterpenes, stypoquinonic acid, taondiol and atomaric acid were also isolated [44].



3: Cavernolide

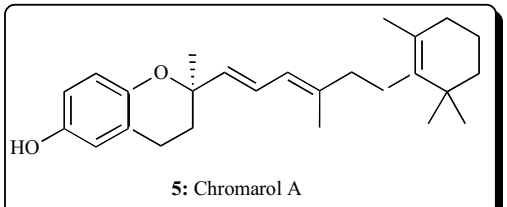
Cholbi and coworkers [45] investigated the marine diterpene ircinin for its effects on secretory and cytosolic PLA_2 activities *in vitro* as well as for inhibition of cellular functions in human neutrophils and inflammatory response in mice. Ircinin is a new inhibitor of PLA_2 activity and these results suggest a potential role for this marine product as an inhibitor of inflammatory processes. Cavernolide (**3**) is a novel C-21 terpene lactone isolated from the sponge *Fasciospongia cavernosa* [46]. Cavernolide inhibited human synovial PLA_2 and decreased the myeloperoxidase degranulation process using different stimuli. Cavernolide also inhibited TNF-α, NO and PGE_2 production in intact cell experiments. NO and PGE_2 reduction was the consequence of the inhibition on iNOS and COX-2 expression.

The inhibitory effects were studied of a series of six cycloamphilectenes, novel marine diterpenes based on amphilectene skeletons and isolated from the Vanatua sponge *Axinella* spp., on NO, PGE_2 and TNF-α production in murine peritoneal macrophages [47]. These compounds strongly reduced NO production in a concentration-dependent manner. Cycloamphilectene 2 (**4**), which is an inhibitor of the NF-κB pathway, also exhibited topical anti-inflammatory

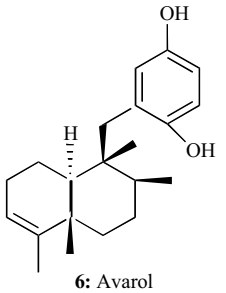


4: Cycloamphilectene 2

activity. A screening of marine sponges revealed that crude extracts of *Psammocinia* spp. exhibited potent 15-LOX inhibitory activity [48]. Bioassay-guided fractionation led to the isolation of chromarols A-E (**5**) as potent and selective inhibitors of 15-LOX. The 6-hydroxychromone moiety found in chromarols A-D was identified as essential for the selective redox inhibition of 15-LOX. Examples of other anti-inflammatory diterpenes of marine sponge origin also included (8*E*, 13*Z*, 20*Z*)-strobilinin and (7*E*, 13*Z*, 20*Z*)-felixinin from a marine sponge *Psammocinia* spp. [49], and novel anti-inflammatory spongian diterpenes from the New Zealand marine sponge *Chelonaplysilla violacea* [50].



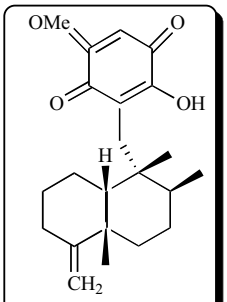
5: Chromarol A



6: Avarol

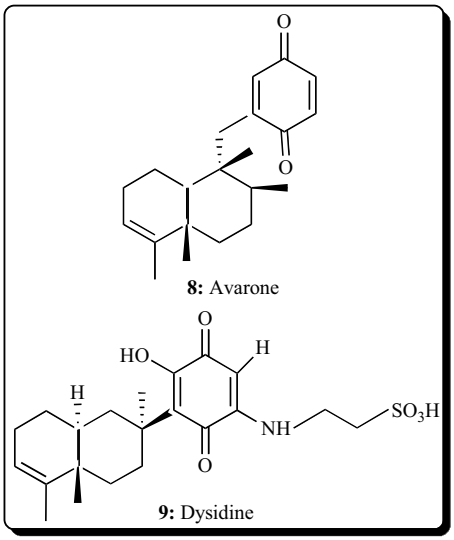
Marine organisms have also been intensively examined for their sesquiterpene content. Among all metazoans sponges are known to produce the largest number of bioactive compounds. Since the early years of research into natural marine products, marine sponges have been the source of an impressive number of novel sesquiterpenes which possess

new carbocyclic skeletons and unusual functionalities. Many new metabolites of mixed biosynthesis have also been isolated from marine sponges. Featured among these is a large array of sesquiterpene/benzenoids, some of the earliest examples of which include avarol (**6**), spongiaquinone and ilimaquinone (**7**). Reports on the anti-inflammatory activity of sponge sesquiterpenes have been found in the literature.



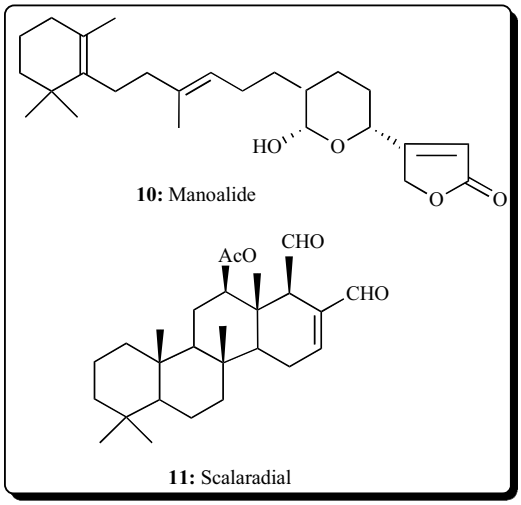
7: Ilimaquinone

Dysidea avara is a sponge species which has yielded new metabolites for more than 20 years, and no doubt further collections from different locations will continue to reveal new chemistry. The terpenoid metabolites reported from *Dysidea* spp. are predominantly sesquiterpenes. Ferrandiz and coworkers [51] investigated the anti-inflammatory activity of avarol (**6**) and avarone (**8**), two sesquiterpenoids isolated from the Mediterranean sponge *Dysidea avara*. Both compounds potently inhibited paw edema induced by carrageenan, as well as ear edema induced by PMA in mice. Avarol and avarone effectively controlled acute inflammation in experimental models after either oral or topical administration, and their anti-inflammatory activity may result from the inhibition of eicosanoid release and depression of superoxide generation in leukocytes. Muller and coworkers [52] introduced the *in vitro* culture of primmorphs from the marine sponge *Dysidea avara*, and demonstrated that this special form of sponge cell aggregates produces avarol.



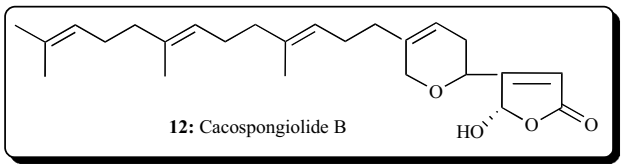
Two new sesquiterpene cyclopentenones, dysidenones A and B, and a new sesquiterpene aminoquinone, dysidine (**9**), all containing the same rearranged drimane skeleton, have been isolated from another *Dysidea* spp. sponge [53]. These compounds significantly inhibited human synovial PLA_2 and modulated other human leukocyte functions such as the degranulation process measured as elastase release and the superoxide production measured by chemiluminiscence. Posadas and coworkers [54] investigated the anti-inflammatory activity of a new bioactive sesquiterpenoid, named dysidotronic acid, isolated from *Dysidea* spp. Dysidotronic acid inhibited the production of TNF-α and IL-1 as well as the production of NO, PGE_2, and LTB_4. Decreased NO generation was the consequence of inhibition of the expression of iNOS, whereas PGE_2 and LTB_4 reduction was due to inhibition of AA bioavailability through a direct inhibitory effect of dysodotronic acid on secretory PLA_2. Plakolide A, a new γ-lactone from the marine sponge *Plakortis* spp., was also found to inhibit iNOS activity [55]. Examples of other anti-inflammatory sesquiterpenes of marine origin also included the sesquiterpene cymopol [56], and ilimaquinone (**7**), a marine sponge metabolite which inhibited DNA binding of NF-κB [57].

Marine organisms, especially sponges, have also provided a large number of biologically anti-inflammatory active sesterterpenoids. The sesterterpenes are the smallest class of terpenoid compounds and consist of alcohol, aldehyde and ketone derivatives of terpene hydrocarbons. It has been reported that some unsaturated aldehyde sesterterpenoids inhibit PLA_2, which catalyses hydrolysis of the ester linkage at the sn-2 position of glycerophospholipids [58]. Since the release of AA from glycerophospholipids is the rate-limiting step in the production of eicosanoid mediators of inflammation, the inhibitory mechanism of PLA_2 by these aldehyde sesterterpenoids, some of them from marine origin, has been of biochemical and medicinal interest. Some of the earliest examples of these sesterterpenoids include manoalide (**10**) and scalaradial (**11**) [59]. Manoalide and scalaradial also inhibited the release of IL-1 and TNF-α from LPS-stimulated human monocytes, and inhibited LPS-induced endogenous PGE_2 production [60, 61].



Manoalide (**10**) is a potent anti-inflammatory sesterterpene isolated in 1980 from the marine sponge *Luffariella variabilis*. Manoalide has been reported to inactivate PLA_2

from several sources as well as to inhibit synthesis of eicosanoids in human polymorphonuclear (PMN) leukocytes [62]. This compound also reduces chemically-induced inflammation *in vivo*. The anti-inflammatory activity of manoalide is due to inhibition of PLA_2 through irreversible binding to several lysine residues [63]. The binding occurs by means of the two masked aldehyde functions present in the polar part of manoalide. Of the two aldehyde groups of manoalide, only the group present in the γ-hydroxybutenolide ring seems to be essential, since cacospongiolides, naturally-occurring analogues lacking the second masked aldehyde group, were also shown to be irreversible PLA_2 inhibitors. Cacospongiolide B (**12**) is a marine sesterterpene isolated from the sponge *Fasciospongia cavernosa* [64]. In *in vitro* studies, this compound inhibited PLA_2 showing selectivity for secretory PLA_2 versus cytosolic PLA_2, and its potency on the human synovial enzyme was similar to that of manoalide. This activity was confirmed *in vivo* in the zymosan-injected rat air pouch, mouse ear edema induced by PMA and on carrageenan paw edema in mice. In order to develop new anti-inflammatory sesterperpenes, manoalide-type compounds are chemically sinthesised [65, 66]. The activity of synthetic analogues of cacospongiolide B against bee venom PLA_2 suggest that the cacospongiolides have enantiospecific interactions with the enzyme that may be independent of the γ-hydroxybutenolide moiety [67].

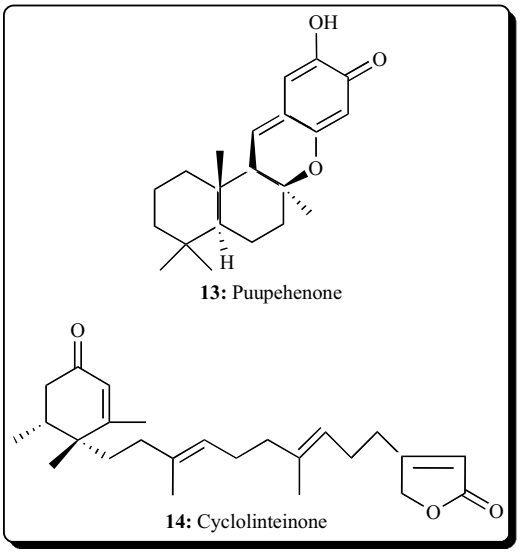


12: Cacospongiolide B

Many manoalide analogues have been isolated from other marine sponges, most of them showing PLA_2 inhibitory properties. Inhibition of secretory PLA_2 by the marine sesterterpenoids cladocorans A and B and their diastereomers almost equalled that of manoalide [68]. Petrosaspongiolides are other anti-inflammatory sesterterpenes isolated from the Caledonian marine sponge *Petrosaspongia nigra*. Petrosaspongiolide M is an inhibitor of PLA_2, showing selectivity for secretory PLA_2 [69]. Inhibition of PLA_2 was also observed *in vivo* in the zymosan-injected rat air pouch and in carrageenan paw edema in mice [70]. The inflammatory response of adjuvant arthritis was reduced by petrosaspongiolide M, which also inhibited LTB_4 levels in serum and PGE_2 levels in paw homogenates.

New and interesting anti-inflammatory sesterterpenes reported in recent years from marine sponges included the scalaradial group. Scalaradial (**11**) is a marine sesterterpene isolated from the sponge *Cacospongia* spp. The scalaradial group of marine metabolites exhibits potent biological activity, mainly anti-inflammatory properties. Scalaradial and other scalaranes were found to completely inactivate the enzyme PLA_2 from bee venom directly and irreversibly [71, 72]. The role of the α,β-unsaturated aldehyde in the inhibition of PLA_2 by scalaradial was investigated. The results demonstrate that the reactivity of the α,β-unsaturated aldehyde of scalaradial is not absolutely essential to its ability to inhibit PLA_2 and lipid mediator production in the intact cells, but adds significantly to its inhibitory potency. Scalaradial also exerts anti-inflammatory effects *in vivo* in the zymosan air pouch and inhibited zymosan stimulated myeloperoxidase release *in vitro* [73]. A series of homoscalarane and scalarane compounds have also been isolated from two distinct species of Pacific nudibranchs *Glossodoris sedna* and *Glossodoris dalli* [74]. These compounds showed moderate activity to inhibit mammalian PLA_2. Marine sesterterpenoids, such as puupehenone (**13**) and hyrtenone A, also showed high potency against 12-human, 15-human and 15-soybean LOX [75]. Additionally, puupehenone was effective in trapping the free radical DPPH, inhibiting Fe^{2+}/ascorbate-induced oxidation of lipids from rat-brain homogenates, and inhibiting oxidation of linseed oil [76].

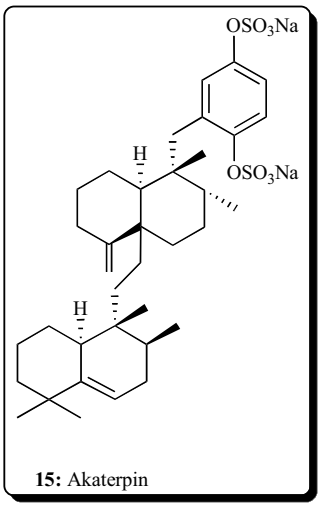
Several other marine organisms and microorganisms have been investigated in the last decade in the search for novel anti-inflammatory sesterterpene molecules. D'Acquisto and coworkers [77] investigated the effect of cyclolinteinone (**14**), a sesterterpene from the Caribbean sponge *Cacospongia linteiformis* on iNOS and COX-2 protein expression in LPS-stimulated J774 macrophages. These results show that cyclolinteinone down-regulates iNOS and COX-2 protein expression by inhibiting NF-κB activation, and suggest that it may represent a novel anti-inflammatory compound capable of controlling the excessive production of PGs and NO occurring in several inflammatory diseases. Mangicols represent a new class of sesterterpene polyols isolated from a marine fungus of the genus *Fusarium* [78]. The mangicols, which possess an unprecedented spirotricyclic skeletal component, showed significant anti-inflammatory activity in the PMA-induced mouse ear edema model.



13: Puupehenone

14: Cyclolinteinone

Triterpenoids and carotenoids are a minor group of marine metabolites; however, few of them have been shown to possess anti-inflammatory activity. Examples include akaterpin (**15**), an inhibitor of phosphatidylinositol-specific phospholipase C, which was isolated from the marine sponge *Callyspongia* spp. [79], and triterpene glycosides from the sea cucumber *Telenata ananas* [80]. In the carotenoid group, examples include the carotenoids from *Dunaliella salina*, a green microalga [81], and the red pigment RP-063 produced



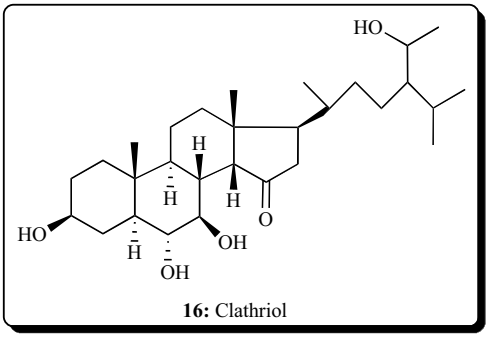
15: Akaterpin

by the marine bacterial strain MS-02-063 from the coastal area of Nagasaki Prefecture, Japan, which showed inhibition of superoxide generation by PMA-stimulated mouse macrophage cell line RAW 264.7 [82].

STEROIDS

Since the start of the twentieth century, steroids have continued to be the focus of the research activities of natural product chemists, synthetic chemists, biochemists and clinicians. The reasons are several-fold and related to the fascination of the chemical complexity of sterols and their biochemical functions in living organisms.

Marine organisms have been found to be storehouses of sterols, particularly in terms of unique side-chain structures and unusual functionalisation. Highly functionalised steroids featuring biogenetically unprecedented structures have been found in a vast array of marine organisms. It has been hypothesised that marine organisms affect the chemical modification of their dietary precursors in order to produce the diverse variation in steroidal content obtained from these sources. Extensive studies on sterols of marine origin during the past decade have resulted in the identification of a plethora of unusual forms with interesting biological activities, including anti-inflammatory properties. For example, clathriol (**16**) is a highly oxygenated steroid with the unusual 14β-configuration, isolated from the New Zealand marine sponge *Clathria lissosdera* [83]. Clathriol showed *in vitro* anti-inflammatory activity against human neutrophil and rat



16: Clathriol

mast cells. The apolar fraction of the crude alcoholic extract of the sponge *Euryspongia* spp. was shown to display anti-inflammatory activity. Bioassay-guided fractionation led to the isolation of the compounds petrosterol (3β-hydroxy-24-narchol-5-en-23-oic acid) which has never yet been found as a natural substance and a new steroid, 3β-hydroxy-26-*nor*-campest-5-en-25 oic acid [84]. The compounds were active for their anti-inflammatory activity against 6-keto-$PGF_{1\alpha}$ release in a human keratinocyte cell line HaCa T.

Other marine organisms, such as algae and gorgonians, also yielded bioactive anti-inflammatory steroids. The marine green alga *Ulva lactuca* was shown to contain 3-*O*-β-*D*-glucopyranosil-stigmata-5,25,-dien sterol, with topical anti-inflammatory activity in the mouse ear edema [85]. Anti-inflammatory steroids were also isolated from another green alga, *Chlorella vulgaris* [86]. These compounds also inhibited PMA-induced inflammation in mice. Calicoferols are 9,10-secosteroids isolated from gorgonians of the genus *Muricella* collected from Jaeju Island, Korea, which exhibited significant inhibitory activity against PLA_2 [87], while from the gorgonian *Pseudopterogorgia* spp., new 9,11-secosteroids with moderate inhibitory activity against PKC were isolated [88]. Anti-inflammatory steroids, such as analogues of gorgosterol and ergosterol, were also isolated from the soft coral *Capnella lacertiliensis* [89], while a new hemiketal steroid named cladiellin A isolated from the soft coral *Cladiella* spp., showed antioxidant activity [90].

ALKALOIDS

Alkaloids represent a group of natural products that has had a major impact throughout history on the economic, medical, political and social affairs of humans. Alkaloids are difficult to define because they do not represent a homogeneous group of compounds from either the chemical, biochemical or physiological viewpoint. Consequently, except for the fact that they are all organic nitrogenous compounds with a limited distribution in nature, reservations must be appended to any general definition.

Marine organisms are known to be a rich source of alkaloids with unique chemical features and pronounced chemical activities, all of which suggests their potential value as lead structures for the development of new pharmaceuticals. Many of these compounds have potent pharmacological effects, including anti-inflammatory and antirheumatic properties. Several classes of alkaloids have been isolated from a variety of marine organisms. Among marine anti-inflammatory alkaloids, the bromopyrrole alkaloids currently seem to be the largest group, with most compounds being isolated from sponges. Hymenialdisine was the first example of a brominated pyrrole alkaloid showing interesting anti-inflammatory activity. Several species of sponges contain hymenialdisine which has been shown as a potent inhibitor of NF-κB and ILs production [91]. Badger and coworkers [92] investigated the effect of hymenialdisine on IL-1 induced proteoglyycan degradation, PG synthesis, NO production and iNOS gene expression in bovine articular cartilage and cartilage-derived chondrocytes. Hymenialdisine inhibited IL-1 stimulated proteoglycan breakdown and NO production in bovine articular cartilage. These results suggest that compounds with this profile may have utility in the

treatment of osteoarthritis. Hymenialdisine also inhibited NO production and iNOS in human cartilage and primary chondrocyte cultures [93].

Exposure of human rheumatoid fibroblasts to IL-1β results in the coordinated up-regulation of PLA_2 and mitogen-inducible COX-2 and the subsequent biosynthesis of PGE_2. Hymenialdisine has been characterised as an inhibitor of NF-κB activation and its exposure to IL-1-stimulated human rheumatoid synovial fibroblasts inhibited PGE_2 production [94]. In addition, hymenialdisine inhibited IL-6 production and reduced IL-8 production dependent on synovial cell strains [95]. Specificity of action is suggested as Il-1 stimulated IL-8 production, which is known to be an NF-κB regulated event, was also inhibited by hymenialdisine [96]. Taken together, hymenialdisine inhibits IL-1-stimulated human rheumatoid fibroblast PGE_2 formation, acting predominantly through the modulation of NF-κB activation, and offers an interesting novel tool for evaluating the role of NF-κB in inflammatory diseases. Other aldisine-type alkaloids with potent anti-inflammatory activity were also recently isolated from the Philippine sponge *Stylissa massa* [97], while the marine sponges of *Agelas* species yielded nagelamides A-H, new dimeric bromopyrrole alkaloids [98]. From another *Stylissa* species, the Australian marine sponge *Stylissa flabellata*, Buchanan and coworkers [99] isolated two new bisimidazo-pyrano-imidazole bromopyrrole ether alkaloids, stylissadines A and B, as their specific bioactive anti-inflammatory constituents.

Other types of marine anti-inflammatory alkaloids included pyridinium and imidazole alkaloids. De Marino and coworkers [100] isolated four bioactive pyridinium alkaloids, spongidines A-D (**17**), from a Vanatua sponge of the genus *Spongia*. These compounds mainly inhibited human synovial PLA_2. Three imidazole alkaloids, leucettamines A and B and leucettamidine, were isolated from the Palauan sponge *Leucetta microraphis* [101]. Leucettamine A and leucettamidine showed potent LTB_4 receptor binding activity, while leucettamine B was inactive. With leucettamine A identified as a pure LTB_4 receptor antagonist, a new structure lead is opened up in inflammatory therapy. Other anti-inflammatory imidazolone-containing alkaloids were also isolated from the New Zealand ascidian *Pycnoclavella kottae* [102].

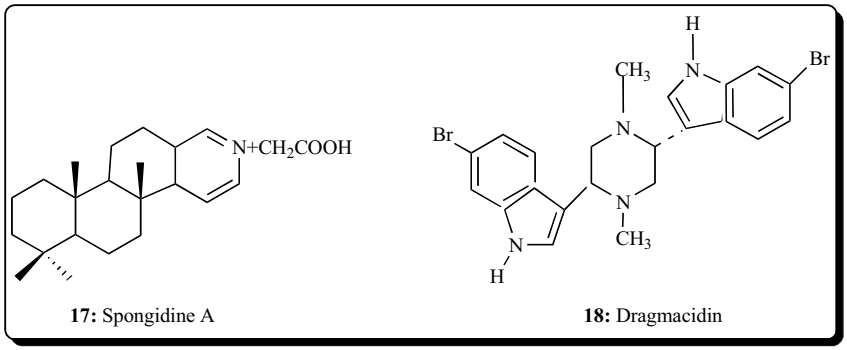
From the Southern Australian sponge *Spongorosites* spp., a new class of marine alkaloids, dragmacidins (**18**), have been reported to be potent inhibitors of protein phosphatases [103]. From the colonial zoanthid *Zoanthus* spp., zoanthamine-type alkaloids have been reported as good candidates for osteroporotic drugs [104, 105]. Yamaguchi and coworkers [106] examined the effect of norzoanthamine hydrochloride on bone weight, strength and morphology in mice. Based on these results, norzoanthamine hydrochloride may act as both a suppressor of bone resorption and an enhancer of bone formation *in vivo*.

Other marine organisms and microorganisms such as tunicates, ascidians, dinoflagellates and fungi also yielded bioactive anti-inflammatory alkaloids. Yondelis (trabectedin) is a novel antitumour agent of marine origin extracted from the tunicate *Ecteinascidia turbinata*. Allavena and coworkers [107] investigated the immunomodulatory properties of yondelis on leukocytes. The *in vitro* production of inflammatory mediators such as IL-6, was markedly reduced by yondelis in monocytes, macrophages, tumour-associated macrophages and freshly isolated ovarian tumour cells. In view of the protumour activity of tumour-associated macrophages and of the strong association between chronic inflammation and cancer progression, the inhibitory effect of yondelis on macrophage viability, differentiation and cytokine production is likely to contribute to the antitumour activity of this agent in inflammation-associated human tumours.

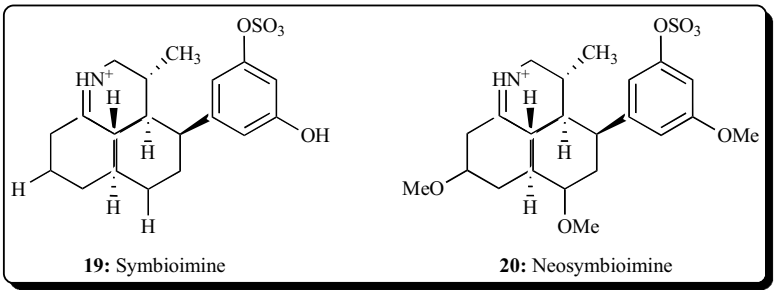
Two amphoteric iminium alkaloids, symbioimine (**19**) and neosymbioimine (**20**), were isolated from a cultivated symbiotic marine dinoflagellate *Symbiodinium* spp. [108]. These compounds have a characteristic 6,6,6-tricyclic iminium ring and an aryl sulphate moiety. Symbioimine significantly inhibited COX-2 activity. Examples of other anti-inflammatory marine alkaloids also included meridianins, a new family of PKC inhibitors isolated from the ascidian *Aplidium meridianum*, from the South Georgia Islands [109], and a new diketopiperazin alkaloid golmaenone, and related alkaloids such as neoechinulin A, isolated from the culture broth of the marine-derived fungus *Aspergillus* spp., which exhibited a significant radical scavenging activity against DPPH [110].

PEPTIDES AND PROTEINS

Proteins and peptides have been used as drugs for many years. The term "peptide" includes a wide range of compounds varying from low to very high molecular weights, and showing marked differences in physical, chemical and pharmacological properties. Proteins are polymers of amino acids joined together by peptide bonds. The distinction be-



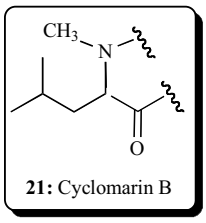
17: Spongidine A **18:** Dragmacidin



19: Symbioimine **20:** Neosymbioimine

tween proteins and peptides is the length of the amino acid chain and molecular weight and is somewhat arbitrary, but generally polypeptide chains in excess of 50 to 75 amino acids are considered proteins instead of peptides.

Marine environments are a well-established source of unique and anti-inflammatory active peptides. Complex cyclic peptides and depsipeptides have emerged as an important class of metabolites present in extracts of marine organisms and microorganisms. For example, cyclomarins A-C (**21**) are new anti-inflammatory cyclic peptides produced by the marine bacterium *Streptomyces* spp. [111]. These compounds, which contains three common and four unusual amino acids, display significant anti-inflammatory activity in both *in vivo* and *in vitro* assays. A novel diketopiperazine exocellular peptide named cyclo-*D*-pipecolinyl-*L*-isoleucin was isolated from the cell-free culture supernatant of the Antarctic psychrophilic bacterium *Pseudoalteromonas haloplauktis* strain TAC125 [112]. The potential antioxidant activity was evaluated by a DPPH free radical scavenging assay. Chemical investigations of the marine red alga *Ceratodictyon spongiosum* containing the symbiotic sponge *Sigmadocia symbiotica* collected from Biaro Island, Indonesia, yielded a new and bioactive thiazole-containing cyclic heptapeptide, cerastospongamide [113]. Cerastospongamide exhibits potent inhibition of PLA_2 expression in a cell-based model for anti-inflammation.

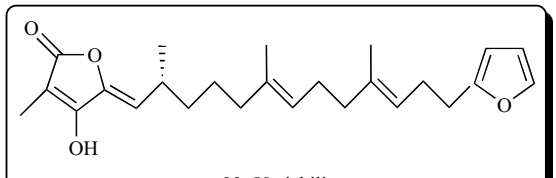


21: Cyclomarin B

Anti-inflammatory peptides isolated from the marine environment also included depsipeptides and lipopeptides. Depsipeptides are bio-oligomers composed of hydroxy and amino acids linked by amide and ester bonds. Many marine depsipeptides show very promising biological activities, including anti-inflammatory properties [114]. Halipeptins A and B are two novel potent anti-inflammatory cyclic depsipeptides isolated from the Vanatua marine sponge *Haliclona* spp. [115]. Halipeptins are novel 17-membered cyclic depsipeptides, consisting of five residues including two alanines and three new residues that appear to be previously undescribed from natural sources. These compounds were shown to possess very potent anti-inflammatory activity *in vivo*. Anti-inflammatory depsipeptides such as salinamides A-E, were also isolated from a marine *Streptomyces* spp. [116, 117]. Fermented marine blue mussel (*Myrtilus edulis*) derived peptides were purified [118]. A hepta-peptide sequence was found to be highly effective for radical scavenging activity. Under the assay conditions, this peptide could scavenge superoxide (98%), hydroxyl (96%), carbon-centred (91%) and DPPH radicals (72%) at 200 μg/ml. The compound also exhibited a strong lipid peroxidation activity at 54 μM.

Marine algae are known for their ability to produce a great diversity of unique secondary metabolites, especially lipopeptides which incorporate modified amino acid moieties, some of which exhibit anti-inflammatory properties. Zhang and coworkers [119] investigated the anti-inflammatory effects of microcolin A, a lipopeptide extracted from the marine blue green alga *Lyngbya majuscula*. Mixed lymphocyte reaction, auto-immunoglobulin M and PMA plus ionomycin stimulation of murine splenocytes were all similarly suppressed by microcolin A. These results indicate that microcolin A is a potent immunosuppressive agent. Additionally, microcolin A significantly inhibited lymphocyte function-associated molecule-1 and intercellular cell adhesion molecule-1 mediated cell adhesion [56].

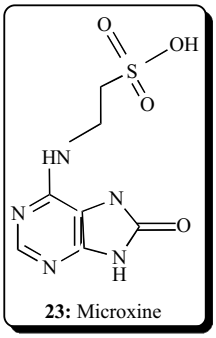
Besides peptides, marine organisms have been reported to produce anti-inflammatory active proteins, which are probably involved in the protection of organisms against physiological and stress conditions. The marine protein variabilin (**22**) has been shown to be a potent dual inhibitor of human secretory and cytosolic PLA_2 with anti-inflammatory activity [120]. An IL-6 cytokine family antagonist protein was reported from the marine sponge *Callyspongia* spp. [121]. *Telesto riisei*, an octocoral from Hawai, produces highly functionalised prostanoids, the punaglandins, which are characterised by various oxygenations and a –12 and –10-chloro-9-cyclopentenone moiety [122]. The punaglandins have shown anti-inflammatory activity. Another coral, the fire coral *Millepora platyphylla*, yielded milleporin-1, a new PLA_2 active protein [123].



22: Variabilin

Phycocyanin is a biliprotein isolated from the microalga *Spirulina* which contains open chain tetrapyrroles with possible scavenging properties Romay and coworkers [124, 125] demonstrated that phycocyanin exerts anti-inflammatory activity in several animal models of inflammation. Phycocyanin significantly reduced ear edema induced by AA and PMA in mice, as well as carrageenan-induced rat paw edema. Phycocyanin also exerted an inhibitory effect in the cotton pellet granuloma test, and inhibited liver microsomal lipid peroxidation as well as edema index in glucose oxidase-induced inflammation in mouse paw. Other investigations showed that the anti-inflammatory effects of phycocyanin may occur, at least partially, through inhibition of PGE_2 production and a moderate inhibition of PLA_2 activity, as well as through inhibition of histamine release from mast cells [126, 127]. Zhou and coworkers [128] investigated the effects of different factors on the antioxidant activity of phycocyanin. This study showed that the phycobilin moiety is the main part of the molecule involved in scavenging hydroxyl radicals.

Amino acids occur in plants and animals, both in the free state and as the basic units of proteins and other metabolites. A few reports on the anti-inflammatory activity of amino acid derivatives from marine sources have been reported in the literature. From the marine sponge *Stylotella aurantium*, a family of anti-inflammatory bisguanidines, palau'amines, were isolated [129, 130], while the Australian marine sponge *Microxina* spp. yielded microxine (**23**), a new purine derivative with inhibitory activity against PKC [131].

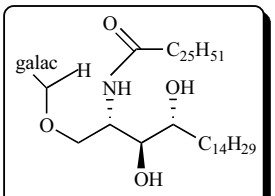


23: Microxine

PHOSPHOLIPIDS

Marine fatty acids are of interest for the different roles and biological properties they exhibit in the cells of marine organisms. Some of these fatty acids have displayed interesting biological activities. Lipids are esters of long-chain fatty acids and alcohols or of their closely related derivatives. The chief difference between these substances is the type of alcohol; in fixed oils and fats, glycerol combines with the fatty acids; in waxes, the alcohol has a higher molecular weight, e.g., cetyl alcohols.

Sphingolipids have received much attention in recent years after the discovery of PKC inhibition by sphingolipids, and indirect evidence leading to the hypothesis that sphingolipid-derived product may function as second messengers. These compounds were first isolated from the soft coral *Sinularia leptoclados* [132], but also from the marine soft corals *Sinularia crassa* [37]. Ceramides (**24**) are lipids consisting of fatty acid and sphingosine with an amine bound with immunostimulatory activities [133-135]. The signalling roles of ceramide, sphingosine and their derivatives are receiving a great deal of attention in biochemical and biomedical research, and have led to the possibility of their use as therapeutics in the treatment of inflammatory diseases.



24: Ceramide

α-Galactoglycosphingolipids, such as agelasphin, are unique immunostimulatory glycosphingolipids from marine sponges. Analysis of the glycosphingolipid composition of the marine sponge *Axinella damicornis* revealed the presence of a new α-galactoglycosphingolipid, damicoside, which is the first of these type of compounds with a glycosylated galactose 4-hydroxy group [136]. This compound exhibited a stimulatory activity comparable to that of agelasphin, showing that a free galactose 4-hydroxy group is not essential for the immunostimulatory activity of α-galactoglycosphingolipids.

Long-chain Ω-3-fatty acids, which are present in marine sources, represent a unique and novel group of nutraceuticals because of their proven multiple therapeutic effects, including anti-inflammatory functions [137]. From the marine alga *Dictyochloris fragrans*, Golik and coworkers [138] isolated sulfonoquinovosyl dipalmitoyl glyceride which inhibited the cell adhesion processes that play important roles in the development of inflammatory-mediated disease states. Novel sulfonoglycolipids, active in the constitutive NOS assay, were isolated from the brown alga *Dictyota ciliolata* [139]. Another brown seaweed, *Undaria pinnatifida*, yielded two anti-inflammatory Ω-3 polyunsaturated fatty acids, which were active against mouse ear inflammation induced by PMA [140]. Berge and coworkers [141] investigated the *in vitro* anti-inflammatory activity of a sulfoglycolipid isolated from the red alga *Porphyridium cruentum*. Results demonstrated that this compound strongly inhibited the production of superoxide anion generated by peritoneal leukocytes primed with PMA. Willis and De Vries [142] reported the isolation from an Australian calcareous sponge of a C30 bis-amino, bis-hydroxy polyunsaturated lipid which inhibits PKC. The compound, which was given the trivial name BRS1, represents a novel PKC inhibitor.

As we can see above, polyunsaturated fatty acids are known to play a role in the prevention of the inflammatory response. Marinosomes are liposomes based on natural marine lipid extracts. Recently, Cansell and coworkers [143] demonstrated that marinosomes contribute to reduce inflammation induced by croton oil by regulating PGE_2 and IL-8 production in human keratinocyte cultures. However, the preventive effect of marinosomes was highly dependent on the lipid concentration used and the liposome mean diameter.

In the marine environment, several polyacetylenic compounds which are biogenetically related with fatty acids have been reported in the last decade. These types of molecules, with interesting anti-inflammatory properties, have been isolated mainly from marine sponges of the genus *Petrosia* spp. Biologically active polyacetylenes characterised by unbranched long alkyl chains have frequently been isolated from these marine sponges. For example, petrocortynes D-H are novel C-46 polyacetylenes isolated from a sponge of the genus *Petrosia* spp. collected from Keomum Island, Korea, which exhibited strong inhibitory activity against PLA_2 [144]. More recently, Hong and coworkers [145] investigated the *in vitro* anti-inflammatory effects of a C_{46} polyacetylenic alcohol, petrocortyne A, isolated from *Petrosia* spp., on various cellular inflammatory phenomena using the macrophage and monocytic cell lines RAW 264.7 and U937. Petrocortyne A strongly blocked TNF-α production in LPS-activated RAW 264.7 cells and PMA/LPS-treated U937 cells. It also blocked NO production in LPS- or interferon-γ-treated RAW 264.7 cells.

POLYSACCHARIDES

Polysaccharides are polymers of monosaccharides (sugars) linked together through glycosidic (ether) linkages and represent a structurally diverse class of biological macromolecules. The structural diversity of these compounds arises from the many different sugars and sugar derivatives such as uronic acids found in polysaccharides, and because each sugar can be covalently linked to other sugars through several different positions of the sugar ring. They are used extensively as foods and pharmaceuticals.

Cell walls of the red algae contain large amount of sulfated, water-soluble polysaccharides, with varying levels and patterns of substitution by sulfate, methoxy, pyruvate groups or sugar side chains. Some of these polysaccharides showed interesting anti-inflammatory properties. Sulfated polysaccharides from red microalgae have anti-inflammatory activity *in vitro* and *in vivo*. For example, Garbacki and coworkers [146] investigated the anti-inflammatory properties of polysaccharides extracted from twelve marine cyanobacterial strains belonging to the genera *Phormidium* and *Nostoc*. The screening program identified several strains as producers of anti-inflammatory polysaccharides in the croton oil-induced edema in mice ear skin model. *In vitro*, the polysaccharide material primarily inhibited the migration of PMNs toward a standard chemoattractant molecule, and also partially blocked adhesion of PMNs to endothelial cells [147]. The data suggested that the anti-inflammatory mechanism for the polysaccharide was, at least in part, due to inhibition of circulating immune cell recruitment towards inflammatory stimuli.

Tannin-Spitz and coworkers [148] evaluated the antioxidant properties of the water-soluble polysaccharides of *Poryphyridium* spp. by determining the ability to inhibit the autooxidation of linoleic acid as determined by the standard thiobarbituric acid and ferrous oxidation assays, and oxidative damage to 3T3 cells as determined by the dichlorofluorescin assay. In all three assays, the polysaccharides inhibited oxidative damage in a dose-dependent manner. The sulfate galactan fraction isolated from another red seaweed, *Porphyria haitanensis*, increased the total antioxidant capacity and the activity of superoxide dismutase and gluthathione peroxidase in aging mice [149].

The high-sulfate-containing exopolysaccharide p-KG03 is produced by the microalga *Gyrodinium impudicum* strain KG03 [150]. The immunostimulatory effects of this sulphated polysaccharide were investigated by isolating peritoneal macrophages from mice 10 or 20 days after they had received a single dose of p-KG03 (100 or 200 mg/Kg). The results suggest that p-KG03 has immunostimulatory effects and enhances the tumouricidal activities of macrophages and NK cells *in vivo*. Other anti-inflammatory and immunomodulatory polysaccharides were isolated from the microalgae *Chlorella stigmatophora* and *Phaeodactylon tricornutum* [151]. The crude polysaccharide extracts of both microalgae showed anti-inflammatory activity in the carrageenan-induced paw edema test. In assays of effects on the delayed hypersensitivity response and on phagocytic activity assayed *in vivo* and *in vitro*, the *Chlorella stigmatophora* extract showed immunosuppressant effects, while the *Phaeodactylon tricornutum* extract showed immunostimulatory effects. Sulfated polymannuroguluronate is a novel anti-acquired immune deficiency syndrome drug candidate, now in a phase II clinical trial, which has been isolated from marine brown algae. Recently, Hui and coworkers [152] demonstrated that the compound significantly reversed the transactivator of transcription protein-induced release of pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6, and dose dependently decreased the accumulation of ROS and NO in THP-1 cells.

Besides algae, other marine organisms and microorganisms such as fungus also yielded anti-inflammatory polysaccharides. YCP, a mitogenic polysaccharide, was isolated from the mycelium of the marine filamentous fungus *Phoma herbarum* strain YS4108 [153]. YCP was found to be able to increase phagocytic activity of mice *in vitro* and *in vivo*, indicating that it may be considered to be a potent immunomodulator that could activate macrophages. Yang and coworkers [154] compared the free radical-scavenging properties and antioxidant activity of YCP and its chemically sulfated derivatives. The current data suggest that sulfation of polysaccharide significantly increases its antioxidant activity. EPS2 is another exopolysaccharide isolated from the culture of *Keissleriella* spp. strain YS4108, a marine filamentous fungus, which possesses pronounced protective effects against H_2O_2-induced cell toxicity [155].

MACROLIDES

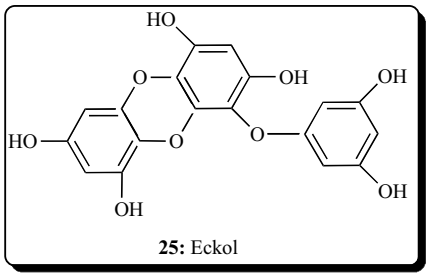
Macrolides are a group of compounds containing a macrocyclic lactone ring, and up to 9 conjugated *trans* double bands. In recent years, new macrolides have been isolated from marine organisms, some of which have been reported to be promising candidates for future drugs. Macrolides constitute an important class of natural anti-inflammatory products of marine origin, especially from marine bryozoa. The bryostatins are a unique family of emerging anti-inflammatory candidates isolated from marine bryozoa. They were first discovered in the bryozoan *Bugula neritina* [156]. Although a novel process was designed for the large-scale isolation of bryostatin from this bryozoan in order to obtain multigram quantities of highly pure material for formulation

studies, preclinical toxicology and clinical trials, problems with supply of sufficient quanties of this natural product hampered the study of this interesting group of marine metabolites for many years. Although the biochemical basis for their therapeutic activity is not known, these macrolactones exhibit high affinities for PKC isoenzymes, compete for the phorbol ester binding site on PKC, and stimulate kinase activity *in vitro* and *in vivo* [157, 158]. Bryostatins bind and activate the cellular receptor for the phorbol ester, and elicit PKC-dependent cellular functions. Such functions include the expression of the IL-2 receptor. Bryostatins also activated *in vitro* PMN and mononuclear cells and triggered human PMNs neutrophil and monocyte oxidative metabolism.

Besides bryozoans, another marine organisms and microorganisms have been reported to produce bioactive macrolides. Jiang and coworkers [159] encountered an unusual actinomycete isolated from a surface inoculum of the Caribbean brown alga *Lobophora variegata*. In saline fermentation, this strain produces two new anti-inflammatory macrolides, lobophorins A and B. The new compounds are potent inhibitors of topical PMA-induced edema in the mouse ear assay when administered either topically or intraperitoneally.

OTHER COMPOUNDS

Reports on the anti-inflammatory activity of compounds of marine origin belonging to other structural types have also been found in the literature. In the marine environment, cyanobacteria represent one of the most prolific sources of bioactive structurally diverse secondary metabolites. Phenolic compounds, occasionally incorporating halogen, occur frequently in these organisms, and reports on their anti-inflammatory activity have been found in the literature. Wiemer and coworkers [160] investigated two new bromophenolic metabolites, vidalols A and B, focussing on those which may function through the inhibition of PLA_2. These compounds were isolated from the Caribbean red alga *Vidalia obtusaloba*. *Ecklonia stolonifera*, which belongs to the brown algae, has been investigated because it is commonly used as a foodstuff in Korea. Five compounds of the phlorotannin type, phloroglucinol, eckstolonol, eckol (**25**), phlorofucofuroeckol and dieckol, isolated from this alga, inhibited total



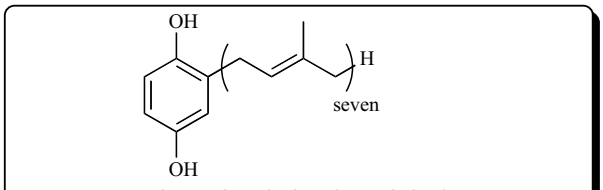
25: Eckol

ROS generation [19]. From another *Ecklonia* species, *Ecklonia cava*, Kim and coworkers [161] isolated several phlorotannins, which inhibit matrix metalloproteinase activity in human dermal fibroblasts and HT1080 cells. Matrix metalloproteinase inhibitors have been identified as potential therapeutic candidates for arthritis and chronic inflammation. Another marine brown alga, *Fucus vesiculosus*, has been shown to contain a new antioxidant isobenzofuranone derivative, which showed 95% DPPH radical scavenging activity [162].

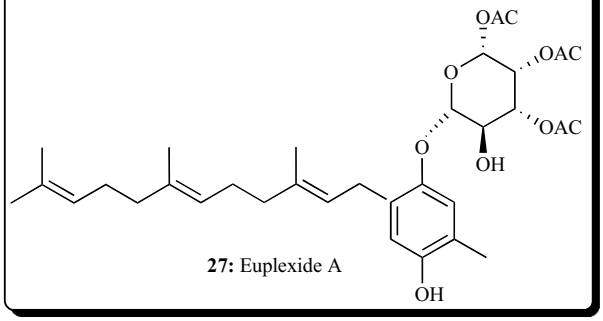
A series of prenyl hydroquinone derivatives isolated from the sponge *Ircinia spinosula* were evaluated for their antioxidant capacity as well as for their effects on inflammatory responses *in vitro* and *in vivo* [163, 164]. These compounds suppressed the production of TNF-α in J774 cells stimulated with LPS and also *in vivo* in the mouse air pouch injected with zymosan. In addition, all prenyl-hydroquinones inhibited the release of nitrite and PGE_2 in LPS-stimulated J774 cells, without direct effects on COX-1, COX-2 or i-NOS activities in several cell-free systems. These compounds were also isolated from the brown alga *Taonia atomaria* [165].

The compounds 2-octoprenyl-1,4-hydroquinone and 2-(24-hydroxy)-octaprenyl-1,4-hydroquinone also showed a significant effect against lipid peroxidation. Gil and coworkers [166] investigated three 2-polyprenyl-1,4-hydroquinone derivatives (**26**) isolated from the Mediterranean sponge *Ircinia spinulosa* for effects on the PLA_2 activity of different origin (Naja Naja venom, human recombinant synovial fluid and bee venom), as well as on human neutrophil function and mouse ear edema induced by PMA. Some structure-activity relationships were established, since differences in the prenylated chain attached to the hydroquinone moiety result in important modifications of these inflammatory responses. Prenylhydroquinone sulfates, which proved to be active against tyrosine PKC, have also been isolated from a marine sponge *Ircinia* spp. collected from New Caledonia [167].

Besides sponges, other marine organisms and microorganisms have been reported to produce anti-inflammatory secondary metabolites. Examples include euplexides A-E (**27**) novel farnesylhydroquinone glycosides isolated from the gorgonian *Euplexara anastomosans* which exhibited moderate antioxidising activity, as well as inhibitory activity against PLA_2 [168, 169], a radical scavenging farnesylhydroquinone isolated from a marine-derived fungus *Penicillium* spp. [170] and new antioxidant hydroquinone derivatives isolated from the algicolous marine fungus *Acremonium* spp. [171].



26: 2-polyprenyl-1,4-hydroquinone derivatives



27: Euplexide A

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