Prostaglandins in Marine Organisms: A Review

Federica Di Costanzo, Valeria Di Dato *, Adrianna Ianora and Giovanna Romano

Marine Biotechnology Department, Stazione Zoologica Anton Dohrn Napoli, Villa Comunale, 80121 Napoli, Italy

* Correspondence: valeria.didato@szn.it; Tel.: +39-081-5833-430

Received: 17 June 2019; Accepted: 19 July 2019; Published: 23 July 2019

Abstract: Prostaglandins (PGs) are lipid mediators belonging to the eicosanoid family. PGs were first discovered in mammals where they are key players in a great variety of physiological and pathological processes, for instance muscle and blood vessel tone regulation, inflammation, signaling, hemostasis, reproduction, and sleep-wake regulation. These molecules have successively been discovered in lower organisms, including marine invertebrates in which they play similar roles to those in mammals, being involved in the control of oogenesis and spermatogenesis, ion transport, and defense. Prostaglandins have also been found in some marine macroalgae of the genera *Gracilaria* and *Laminaria* and very recently the PGs pathway has been identified for the first time in some species of marine microalgae. In this review we report on the occurrence of prostaglandins in the marine environment and discuss the anti-inflammatory role of these molecules.

Keywords: prostaglandins; clavulones; punaglandins; thromboxane; inflammation; marine vertebrates; marine invertebrates; diatoms; macroalgae

1. Introduction

Marine organisms have a great potential to produce a vast variety of bioactive molecules with high antibiotic, anti-proliferative, and anti-inflammatory activity [1]. The biodiversity hosted by the oceans is greater than in terrestrial environments [2] but nonetheless, marine bioresources are still underexplored, and many species await to be discovered.

The high probability to find new interesting bioactive molecules from marine organisms has fostered the effort of the scientific community to adopt new technologies and approaches to increase the success of biodiscovery from marine resources, with a main focus on products with antibiotic, antitumor and anti-inflammatory activities. Of particular interest is the search for new anti-inflammatory compounds since inflammation processes are often related to the onset of chronic pathologies and tumors.

Indeed, inflammation processes represent a fundamental way to restore the original equilibrium of a cell or tissue whose physiology has been impaired by damaging stimuli [3]. At the same time, if inflammation is not blocked it can stimulate a cascade of events that eventually lead to serious diseases such as cancer and autoimmune disorders [4]. The inflammation-resolution process can have different features depending on the type of tissue and injurious stimulus [5], therefore, specific types of pro-resolution stimuli or drugs may be necessary [6]. Both the onset and the resolution of the inflammation are active processes that involve a complex interplay of different molecules [7] like chemokines, cell adhesion molecules, proteolytic enzymes, eicosanoids [8], reactive oxygen species (ROS), and reactive nitrogen species (RNS) [9,10]. Among these, eicosanoids deriving from oxidation of polyunsaturated fatty acids (PUFA) through cyclooxygenase (COX) and lipoxygenase (LOX) pathways play a pivotal role both in the onset and in the resolution of inflammation [9]. The main products of COX enzymes are prostaglandins (PGs), fatty acid derivatives with a molecular structure based on 20 carbon atoms that share a prostanoic acid skeleton.
Prostaglandin E\(_2\) was the first PGs to be identified in the early 1930s in human seminal plasma by Von Euler \[11\] and, independently, by Goldblatt \[12\] although the chemical structures were determined only 30 years later by Bergström, Samuelsson, and co-workers \[13\].

PGs are very well studied and described in mammals where they are active in a great variety of physiological and pathological processes such as smooth muscle and vaso-tone regulation, signaling, hemostasis sleep-wake regulation, reproduction, and especially inflammation. In these organisms, they are synthetized and released in response to external stimuli \[14\] and rapidly inactivated by metabolizing enzymes after they have accomplished their function \[15\].

PGs represent very important and interesting lipid mediators in all vertebrates and in both terrestrial and marine invertebrates \[16,17\]. Plants utilize chemically related molecules (jasmonic acid) that have a defensive role, similarly to PGs \[16,18,19\]. Nevertheless, in some plant species like onions and poplar, a few PGs have also been identified \[20\].

In the marine environment, prostaglandins have been reported both in vertebrates such as carps, sheatfish and leopard sharks, and invertebrates such as sea squirts, mussels, scallops, crawfish, blue crabs, and sea-anemones and in some macroalgae as the red alga \textit{Gracilaria asiatica} C. F. Zhang & B. M. Xia, 1985 and the brown alga \textit{Laminaria digitata} (Hudson) J. V. Lamouroux, 1813.

The earliest report about the presence of prostaglandins in marine invertebrates was by Weinheimer and Spraggin (1969) that discovered 15-epi-prostaglandin A\(_2\) and its acetate methyl ester in the gorgonian-type coral \textit{Plexaura homomalla} Esper, 1794 \[21\]. The discovery of high PGs levels in gorgonians contributed to the rapid growth of the study and application of PGs in the pharmaceutical and biomedical sector \[22\].

Very recently, Di Dato et al. (2017) described the presence of all the three series of PGs molecules also in diatoms, an ecologically successful group of marine microalgae \[23\].

In this review, we present a short background on prostaglandin structure and function and give an updated overview of the presence of PGs in marine organisms, discussing the anti-inflammatory role of PGs from the marine environment.

2. Structure, Biosynthesis, and Activity of Prostaglandins in Mammals

Prostaglandins consist of a cyclopentanone nucleus with two side chains. Primary prostaglandins, which include prostaglandin D\(_2\) (PGD\(_2\)), prostaglandin E\(_2\) (PGE\(_2\)), prostaglandin F\(_{2\alpha}\) (PGF\(_{2\alpha}\)), and prostaglandin I\(_2\) (PGI\(_2\)), contain a 15-hydroxyl group with a 13,14-trans double bond (Figure 1).

Currently, three classes of prostaglandins are categorized, based on the number of double bonds present within the molecule and on the fatty acid precursor. Prostaglandins belonging to the series 1 have one double bond and derive from 8,11,14-eicosatrienoic acid (di-homolinoenic acid, ETrA), those of the series 2 have two double bonds and derive from 5,8,11,14-eicosatetraenoic acid (arachidonic acid, ARA), and those of the series 3 have three double bonds and derive from 5,8,11,14,17-eicosapentaenoic acid (EPA).
Figure 1. Prostaglandin biosynthetic pathway. Enzymes involved in the pathway are reported next to the arrows. For the abbreviation, refer to the text. Modified from [24].

Their nomenclature comprises 10 specific molecular groups, identified by the letters A through J, that differ by variation in the functional groups attached to positions 9 and 11 of the cyclopentane ring. For PGF, the additional subscript “α” or “β” denotes the spatial configuration of the carbon 9 hydroxyl group. For additional details on the nomenclature of prostaglandins see Lands, 1979 [25].

PGs action is mediated by the interaction with specific receptors present on the plasma membrane. These are transmembrane G-protein coupled receptors (GPCR), named as prostaglandin EP receptor (EP), prostaglandin F2α receptor (FP), prostaglandin DP receptor (DP), and prostacyclin I2 receptor (IP) receptors, that are highly selective for PGE2, PGF2α, PGD2, and PGI2, respectively [26]. The EP family comprises four isoforms (EP1-4) that play a relevant role in inflammation processes [27]. The downstream signaling of this receptor family is responsible for the pleiotropic ability of PGE2 to activate different processes, including cell proliferation, apoptosis, angiogenesis, inflammation, and immune surveillance in different cell types [24].

Most prostaglandins display a marked structure-activity specificity mainly determined by substitutions in the cyclopentanone ring and the degree of unsaturation of the side chains. They exert their function once secreted into the extracellular medium, where they are rapidly metabolized by 15-hydroxyprostaglandin dehydrogenase (15-OH-PGDH). This enzyme selectively oxidizes the hydroxyl group at carbon 15 into a 15-keto derivative [28] accompanied by a substantial loss of biological activity.

Prostaglandins derive from the sequential actions of highly specific enzymes (Figure 1). Their synthesis is initiated by phospholipases A2 (PLA2), a family of enzymes that hydrolyze membrane phospholipids at the sn-2 position, liberating free fatty acid precursors, mainly ARA [15]. These enzymes represent a key step in the PG biosynthetic pathway, being regulated by Ca2+ binding and phosphorylation by mitogen-activated protein kinase (MAPK) in response to different stimuli. Membrane-released ARA is then rapidly converted through the cyclization and inclusion of molecular oxygen in the precursor by the action of cyclooxygenase (COXs) enzymes into the unstable metabolite...
PGG$_2$, which is subsequently reduced to PGH$_2$ by the same enzyme [14]. Cyclooxygenases exist in a substrate-limiting environment; thus, liberation of fatty acids from esterified stores results in the prompt formation of the products. There are two major COX isoforms; COX-1 is constitutively active and present in most cells in the body; expression of the COX-2 isoform is inducible in many tissues by pro-inflammatory and mitogenic stimuli, such as cytokines [29]. The specific transformation of the first product PGH$_2$ to other PGs and thromboxanes (TXs) by downstream enzymes is complexly orchestrated and is cell specific, since each cell tends to form mainly one of these compounds as the major product. For example, in brain and mast cells, PGH$_2$ is converted to PGD$_2$, whereas it is converted in PGF$_2\alpha$ in the uterus; from the same precursor, vascular endothelial cells produce PGI$_2$ (prostacyclin) and platelets release thromboxane A$_2$ (TXA$_2$).

The conversion to PGE$_2$, the most widespread PG, is due to PGE synthase-1, also present in different isoforms in mammals: microsomal PGE synthase-1 (mPTGES-1), mPTGES-2, and cytosolic PGE synthase (cPTGES), the latter of particular interest since frequently associated to the tumorigenic activity of PGE$_2$ [30].

Prostaglandin E$_2$ synthesis is a key event for the development of the three principal signs of inflammation: swelling, redness, pain and fever. Moreover, PGE$_2$ also contributes to the amplification of the inflammatory response by enhancing and prolonging signals produced by pro-inflammatory agents, such as interleukin 1$\alpha$ bradykinin, histamine, neurokinins, and complement [31,32]. These signals, in turn, can increase COX-2 expression thus further increasing PGE$_2$ synthesis. This PG, however, can have a double, inverse role, being also able to act as an immunosuppressant, repressing the differentiation of T helper 1 cells and limiting cytokine release and further prostaglandin synthesis by activating a negative feedback on mPGES-1 (Figure 2a).

PGD$_2$-synthesizing enzymes exist as two distinct genes coding for hematopoietic- and lipocalin-type PGD synthases (H-PTGDS and L-PTGDS, respectively). H-PTGDS is generally localized in the cytosol of immune and inflammatory cells, whereas L-PTGDS has a tissue-based expression [33]. The activity of PGD$_2$ has been mainly associated with inflammatory conditions, being involved in immunologically relevant functions. Its action seems to be mediated by the non-enzymatic production of the PGI$_2$ family, which occurs through a spontaneous dehydration in aqueous solutions. One of the most studied PGJ$_2$ metabolites, 15-deoxy-$\Delta^{12}$-PGJ$_2$ (15dPGJ$_2$), showed anti-inflammatory properties based on interaction with the intracellular targets Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), Activator Protein 1 (AP-1), and Peroxisome Proliferator-Activated Receptor gamma (PPAR-γ) [31]. 15dPGJ$_2$ also induces the reduction of neutrophil migration and inhibits the release of Interleukin 6 (IL-6), Interleukin 1$\beta$ (IL-1$\beta$), Interleukin 12 (IL-12), and Tumor Necrosis Factor-α (TNF-α) from macrophages (Figure 2b).

PGD$_2$ can be further metabolized to PGF$_2\alpha$, although the latter can also be synthesized from PGH$_2$ via PGF synthase. PGF$_2\alpha$ acts via FP receptors, resulting in the elevation of intracellular free calcium concentrations that regulates numerous important physiological functions related to reproduction linking multiple molecular mechanisms that are fine-tuned coordinated events in mammalian physiology [34] (Figure 2c). The emerging role of PGF$_2\alpha$ in acute and chronic inflammation has opened new opportunities for the design of novel anti-inflammatory drugs.

A non-enzymatic dehydration reaction is also responsible for the formation of the PGA series from the corresponding PGE. The PG series A and J contain an $\alpha,\beta$-unsaturated carbonyl group within the cyclopentenone ring, which seem to contribute to the anti-inflammatory activity of these PGs [35].

The enzyme prostaglandin I synthase (PGIS), a member of the cytochrome P450 superfamily, specifically converts PGH$_2$ to PGI$_2$ [33]. This PG has anti-mitogenic activity and inhibits DNA synthesis through specific IP receptors. It mediates pro-inflammatory stimuli in non-allergic acute inflammation, while acting as an anti-inflammatory mediator in Th2-mediated allergic inflammatory responses. Soon after having exerted its action, PGI$_2$ is rapidly converted by non-enzymatic processes to the inactive product 6-keto-PGF$_1\alpha$ (Figure 2d).
Figure 2. Prostaglandins and inflammation. (a) Prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) stimulation of inflammatory response. Numbers indicate the sequence of events from PGE\textsubscript{2} synthesis to stimulation of inflammation trough positive feedback on cyclooxygenase (COX)-2 and negative feedback on microsomal PGE synthase-1 (mPTGES-1); (b) The anti-inflammatory role of prostaglandin J\textsubscript{2} (PGJ\textsubscript{2}); (c) prostaglandin F\textsubscript{2\alpha} (PGF\textsubscript{2\alpha}) signaling; (d) prostaglandin I\textsubscript{2} (PGI\textsubscript{2}) signaling. For details, refer to the text.

3. Prostaglandins and Derivative Molecules in Marine Organisms

Similar to terrestrial vertebrates, in marine vertebrates prostaglandins are involved in reproduction, osmoregulation, regulation of oxygenation, and cardiovascular system [36]. Marine invertebrates, including sponges, corals, and molluscs, also contain a wide range of prostaglandins, many of which are of the conventional type (PGA\textsubscript{2}, PGE\textsubscript{2}, PGD\textsubscript{2}, PGF\textsubscript{2\alpha}), with similar functions as in mammals (reproduction, ion transport) and are also probably used as defense compounds [17]. Interestingly, in some invertebrates, PGs are able to perform different actions based on the tissue or compartment localization [37].

Complex marine photosynthesizing organisms, like some genera in the brown, green, and red algal groups (respectively, Laminaria, Euglena, and Gracilaria species) express the cyclooxygenase gene synthesizing PGE\textsubscript{2}, PGF\textsubscript{2\alpha}, and other PGs whose functions are not yet known, but seem to be associated to a defensive role [17].
### 3.1. Corals

Among marine invertebrates, corals represent a very interesting group producing specific PGs that are not present in mammals. The Caribbean gorgonian *Plexaura homomalla* was indeed the species in which PGs were firstly identified in a marine organism, representing also a major source of these compounds in nature [38] (Figure 3a).

![Figure 3. Corals prostaglandins.](image)

Weinheimer A. and Spraggins R. were the first to perform PGs extraction in *P. homomalla*, identifying in its dry cortex 15-epi-PGA₂ and its methyl ester acetate (respectively 0.2% and 1.3%) [15] in an R-configuration on their C-15 asymmetric center, a configuration not present in mammals. In addition to (15R)-epi-PGA₂, also (15R)-PGE₂, its methyl ester and a complex mixture of other prostaglandins were subsequently found by Light R. and Samuelsson B. [39]. However, these molecules were found also in S configurations [40] and the occurrence of one of the two seems to be related to the geographical distribution of *P. homomalla* [38].

The high PGs concentration in these invertebrates stimulated the attempt to use them as precursors for the chemical synthesis of the biologically active prostaglandins A₂, E₂, and F₂α, since their chemical synthesis in large-scale for medical and pharmaceutical purposes was complicated by the necessity of 16 different chemical reactions [41].

The observation that *P. homomalla* present in coral reefs is not commonly eaten by fishes, led Gerhart [42] to hypothesize that the high amount of PGs they contain could be used as chemical defense against potential predators, since it is known that in mammals they can cause vomiting and
nausea when administered orally. Indeed, oral doses of both (15R)-PGA$_2$ and (15S)-PGA$_2$ caused vomiting in a test with fishes, while the PGA$_2$ present in the surrounding water did not cause any effect [42]. However, the hypothesized defensive role seems not to be realistic since PGA$_2$ is stored in coral tissues only as acetoxy methyl esters, whose conversion to (15R)-PGA$_2$ (the compound tested by Gerhart) needs about 24 hours [40]. Moreover, while (15R)-PGA$_2$ inhibits fishes from feeding, the acetoxy methyl ester form, orally delivered, does not show any repellent effect. For this reason, as the process of production of the active (15R)-PGA$_2$ seems too slow to provide the coral with an effective defense mechanism, the function of these molecules in corals is still an open question.

The R-prostaglandins extracted from *P. homomalla* collected on the Island of San Andreas, in the Caribbean Ocean, were also tested in vivo on mouse ear edema induced by 12-O-tetradecanoylphorbol-13-acetate (TPA) and in vitro, in anti-inflammatory screenings as leucocyte degranulation, myeloperoxidase (MPO), and elastase enzymatic activity inhibition. The results showed that (15R)-PGE$_2$ and, to a lesser extent, (15R)-O-AcPGA$_2$ had an anti-inflammatory activity in vivo and in vitro (Table 1). In particular, in the leucocyte degranulation assay, (15R)-PGE$_2$ greatly inhibited the release of both MPO and elastase, while the other prostaglandins tested were moderately active in the inhibition of elastase release but not of MPO [43].

### Table 1. List of the tested effects of marine prostaglandins, and their derivatives, on mammalian cells.

| Prostaglandin       | Producer Organism | Activity                                  | Target Cells                              | Reference                  |
|---------------------|-------------------|-------------------------------------------|-------------------------------------------|----------------------------|
| (15R)-PGE$_2$       | *Plexaura homomalla* | Anti-inflammatory                          | Leucocyte/TPA-induced mouse-ear edema     | Reina et al., 2013 [43]   |
| (15R)-O-AcPGA$_2$   |                   |                                           |                                           |                            |
| Clavulones I-III    | *Clavularia viridis* | Anti-inflammatory                          | Fertilized chicken eggs                   | Kikuchi et al., 1983 [44] |
| Clavulones I-III    |                   | Anti-cancer                               | HL-60                                    | Honda et al., 1985 [45]; Huang et al., 2005 [46] |
| Clavulone II        | *Clavularia viridis* | Anti-viral                                | VSV infected L929                        | Bader et al., 1991 [47]   |
| Chlorovulone I      | *Clavularia viridis* | Anti-proliferative and cytotoxic          | HL-60                                    | Iguchi et al., 1985 [48]  |
| PGs                 |                   |                                          |                                           |                            |
| Epoxy-prostanoids   | *Clavularia viridis* | Anti-proliferative                        | HL-60                                    | Iguchi et al., 1987 [49]  |
| Bromovulone I and   | *Clavularia viridis* | Anti-proliferative and cytotoxic          | HL-60                                    | Iguchi et al., 1986 [50]  |
| Iodovulone I        |                   |                                           |                                           |                            |
| Bromovulone III     | *Clavularia viridis* | Cytotoxic                                 | PC-3/HT-29                               | Shen et al., 2004 [51]    |
| Chlorovulones II    | *Clavularia viridis* | Cytotoxic                                 | PC-3/HT-29                               | Shen et al., 2004 [51]    |
| and III             |                   |                                           |                                           |                            |
| Claviridenone F     | *Clavularia viridis* | Cytotoxic                                 | A549/HT-29/P-388                         | Duh et al., 2002 [52]     |
| Claviridenone G     | *Clavularia viridis* | Cytotoxic                                 | A549                                     | Duh et al., 2002 [52]     |
| Clavirins I-II      | *Clavularia viridis* | Growth-inhibition                         | HeLa S3                                  | Iwashima et al., 1999 [53]|
| Clavubicyclone       | *Clavularia viridis* | Growth-inhibition                         | MCF-7/OVCAR-3                            | Iwashima et al., 2002 [54]|
| Punaglandins I-IV   | *Telesto riisei*   | Cytotoxic                                 | L1210                                    | Baker et al., 1985 [55]   |

*Euplexaura erecta* Kükenthal, 1908 [56] (Figure 3b), *Lobophytum depressum* Tixier-Durivault, 1966 [57] (Figure 3c), and *Gersemia fruticosa* Sars, 1860 [58] (Figure 3d) also produce PGs. Interestingly, PGF$_{2\alpha}$ and its derivatives were principally found in these species: PGF$_{2\alpha}$ in *E. erecta* [56]; (15R)-PGF$_{2\alpha}$-11-acetate methyl ester, its 18-acetoxy derivative compound and their corresponding free carboxylic acids in *L. depressum* [57]; PGF$_{2\alpha}$ and 15-keto-PGF$_{2\alpha}$ together with PGD$_2$, PGE$_2$ in *G. fruticosa* [58].

In addition to the identification of PGs molecules in corals, also the enzyme responsible for their synthesis, the cyclooxygenase, was isolated and characterized for the first time from *P. homomalla* and *G. fruticosa* [59].
3.2. Other Marine Invertebrates

One of the first studies on marine invertebrates, excluding corals, was a comparative analysis done by Christ E. and Van Dorp D., on representative species in the Mollusca (Mytilus), Crustacea (Homarus), and Cnidaria (Cyanea) phyla versus terrestrial animals [60]. The authors were able to find PGs, particularly PGF\(_{1\alpha}\) but only at very low levels. In some cases, the arachidonic acid precursor was also not detectable making it difficult to assert the existence of PGs and their functional role [60]. These results were confirmed in extended studies including more species in the Chordata, Mollusca, Cnidaria, and Crustacea phyla [16,61,62].

With the improvement of instrument sensitivity, it was possible, more than 10 years later, to conduct functional studies on PGs in molluscs (Figure 4a) and crustaceans (Figure 4b).

![Figure 4. Marine invertebrate prostaglandins. (a) Molluscs; (b) Crustaceans; (c) Echinoderms. Except for Tethys fimbria and Aplysia californica, pictures show organisms that are only representatives of each phylum. For details, refer to the text.](image)

Results obtained highlighted different roles for PGs in marine invertebrates, like reproduction, regulation of ion flux, and thermoregulation and fever, mediated respectively by PGF\(_{2\alpha}\), PGE\(_2\), and PGE\(_1\) (Table 2) [63].
Table 2. Update of prostaglandins and its derivatives, and functional roles in marine organisms.

| Compound | Producer Organism | Biological Activities | Reference |
|----------|-------------------|-----------------------|-----------|
| PGF2α    | *Marsupenaeus japonicus* | Ovarian maturation | Tahara et al., 2004 [64] |
|          | *Thunnus thynnus* | Contraction of smooth muscles during ejaculation and metabolism of testis | Nomura et al., 1973 [65] |
| PGE1     | Marine Invertebrates | Thermoregulation and fever | Stanley-Samuelson, 1987 [63] |
|          | *Laminaria digitata* | Protection against stress conditions induced by copper excess | Ritter et al., 2008 [19] |
|          | *Salmo sp.* | Contraction of smooth muscles during ejaculation and metabolism of testis | Chirst and Van Dorp, 1972 [60] |
| PGE2     | *Marsupenaeus japonicus* | Ovarian maturation | Tahara et al., 2004 [64] |
|          | *Paralichthys olivaceus* and *Thunnus thynnus* | Contraction of smooth muscles during ejaculation and metabolism of testis | Nomura et al., 1973 [65] |
|          | *Gracilaria vermiculophylla* | Wounding-activated chemical defense molecules | Nylund et al., 2011 [66] |
|          | *Laminaria digitata* | Protection against stress conditions induced by copper excess | Ritter et al., 2008 [19] |
|          | *Tethys fimbria* | Reproduction and multiple roles depending on body localization | Cimino et al., 1991 [67]; Di Marzo et al., 1991 [37] |
|          | *Oncorhynchus keta* | Contraction of smooth muscles during ejaculation and metabolism of testis | Nomura et al., 1973 [65] |
|          | *Gracilaria vermiculophylla* | Wounding-activated chemical defense molecules | Nylund et al., 2011 [66] |
|          | *Laminaria digitata* | Protection against stress conditions induced by copper excess | Ritter et al., 2008 [19] |
| PGE2-1,15-lactone | *Tethys fimbria* | Reproduction and multiple roles depending on body localization | Cimino et al., 1991 [67]; Di Marzo et al., 1991 [37] |
| PGE2-1,15-lactone-11-acetate | *Tethys fimbria* | Reproduction and multiple roles depending on body localization | Cimino et al., 1991 [67]; Di Marzo et al., 1991 [37] |
| PGD1     | *Laminaria digitata* | Protection against stress conditions induced by copper excess | Ritter et al., 2008 [19] |
| PGA2     | *Gracilaria vermiculophylla* | Wounding-activated chemical defense molecules | Nylund et al., 2011 [66] |
|          | *Laminaria digitata* | Protection against copper stress and trigger of oxidative responses | Zambounis et al., 2012 [68] |
| PGB2     | *Laminaria digitata* | Protection against stress conditions induced by copper excess | Ritter et al., 2008 [19] |
| PGJ2     | *Laminaria digitata* | Protection against stress conditions induced by copper excess | Ritter et al., 2008 [19] |
| Clavulones | *Clavularia viridis* | Suggested to be hypothetical repellents against other marine organisms | Honda et al., 1985 [45] |
| iTXB2    | *Dayatis sabina* | Blood clotting | Cabrera et al., 2003 [69] |
| TXB2     | *Oncorhynchus mykiss* | Vasodilator agent | Thomson et al., 1998 [70] |
In the mollusc *Modiolus demissus* Dillwyn, 1817 the uptake and binding of prostaglandins by gills was investigated, considering that bivalves can both synthetize and accumulate PGs from the surrounding medium [71]. The study revealed the presence of tissue specific, time and pH dependent, PGs binding sites with higher affinity to PGA₂ with respect to PGE₂ or PGF₂α [71].

Moreover, three prostaglandin-lactones (PGE₂-1,15-lactone, PGE₃-1,15-lactone, and PGE₃-1,15-lactone-11-acetate) of the E and F series were identified in the mantle and body, respectively, of the nudibranch mollusc *Tethys fimbria* Linnaeus, 1767 (Figure 4a). High quantities of a complex mixture of PGF₂α and PGF₃α 1,15-lactones fatty acid esters (PLFE) were found in its eggs, particularly in mature ovotestis but not in immature ones suggesting a role for PLFE in mollusc reproduction [67]. Altogether, these results led to hypothesize a multiple biological role of prostaglandin-lactones, precursors of PGEs, as defense allormones, and involved in the control of smooth muscle contraction, and egg production and fertilization, depending on their body localization (Table 2) [37].

Crustaceans (Figure 4b) also use PGs for physiological functions. Indeed, PGE₂ and PGF₂α were identified in the ovary of the prawn *Marsupenaeus japonicus* Spence Bate, 1888 where they participate in ovarian maturation (Table 2) [64] whereas in the crab *Carcinus maenas* Linnaeus, 1758 they are produced in blood cells following a stimulus induced with a calcium ionophore, in the presence of exogenous fatty acids (FA) [72].

Echinoderms (Figure 4c) also represent a source of PGs. Among all the echinoderms analyzed, the starfish *Patinia pectinifera* Muller and Troschel, 1842 had the highest amount of prostaglandins [73]. PGE₂ and PGF₂α have been identified from the sea cucumber *Stichopus japonicus* Selenka, 1867 using TLC [73]. A study conducted with PGs-3H evidenced that the sea urchin *Arbacia punctulata* Lamarck, 1816 could accumulate PGs from the surrounding water into its gut or stomach [74], and to accumulate PGA₁ both in fertilized and unfertilized eggs, with fertilized eggs accumulating more PGs than unfertilized eggs [74].

*Strongyllocentrotus nudus* A. Agassiz, 1864 and *S. intermedius* A. Agassiz, 1864 were also reported to have a PGs-like activity in their inner organs [74].

### 3.3. Marine Vertebrates

As already mentioned, in fish PGs are involved in several processes, such as ovulation, spawning, osmoregulation, regulation of branchial ion fluxes and of the cardiovascular system [36]. Christ and Van Dorp in their comparative studies on PGs considered not only invertebrates, but also fish [60]. They identified moderate yields of PGE₁ in freshwater fish and lower yields in homogenates of gills of *Salmo* sp. [60]. Successively, PGE₂ was identified for the first time in the testis of the flounder *Paralichthys olivaceus* Temminck & Schlegel, 1846, PGF₁α in the semen of the salmon *Oncorhynchus keta* Walbaum, 1792 and PGE₂ and PGF₂α in the testis of the tuna *Thunnus thynnus* Linnaeus, 1758 [65] (Figure 5a).

In order to explain the reason why prostaglandins are present in these marine animals, although they are oviparous, it was suggested that the identified prostaglandins might be used for the contraction of smooth muscle during ejaculation and for the metabolism of testis in lower animals as in mammals (Table 2) [65]. After this study, PGE₂ was isolated and subsequently identified in the gastrointestinal tract and in the skin of the shark *Triakis scyllia* Müller & Henle, 1839 [16,75] (Figure 5b).

In the brook trout *Salvelinus fontinalis* PGE₂ and PGF₂α (Figure 5a) are synthetized in the follicle wall of mature oocytes, but the highest quantity of prostaglandins was found in the extra-follicular tissue [76]. PGE₂ was also found in the skin of *Pleuronectes platessa* Linnaeus, 1758 (Figure 5a) in response to the fungal extract of *Epydermophyton floccosum* (Harz) Langeron & Miloch, 1930 known be an inducer of erythema [77].

Leucocytes of the dogfish *Scyliorhinus canicula* Linnaeus, 1758 secerned high levels of PGE₂, PGD₂ and PGF₂α (Figure 5b) when exposed to the Ca²⁺ ionophore A23187 [78]. PGE₂ and PGF₂α were found in the red blood cells of the toadfish *Opsanus tau* Linnaeus, 1766 [79] (Figure 5a).
3.4. Macroalgae

3.4.1. Red Macroalgae

Marine red algae are rich in C20 polyunsaturated fatty acids that, in animals, are precursors of prostaglandins, thromboxane, and other eicosanoids. Although the presence of the prostaglandin-endoperoxide pathway has been demonstrated in non-mammal marine vertebrates and invertebrates, for a long time less was known about these enzymes in non-animal organisms. The first report about the presence of prostaglandins in macroalgae (Figure 6) described the identification of PGE$_2$ and PGF$_{2\alpha}$ in *Gracilaria lichenoides* Greville, 1830 [80].

The genus *Gracilaria*, that comprises algae used in the food and cosmetic industry, is very rich in ARA, varying from 45.9% and 62.0% of the total FA depending on the season. Among these, *G. vermiculophylla* (Ohmi) Papenfuss, 1967 is one of the algae with the highest content of ARA [81]. This, with other *Gracilaria* species such as *G. asiatica* and *G. chorda* Holmes, 1896, seem to be responsible for a gastrointestinal disorder known as “onogori” poisoning in Japan when it is eaten raw [18]. The possible reason for this poisoning seems to be the fact that the COX contained in raw seaweeds use
the highly unsaturated fatty acids to produce great amounts of PGE₂ in the stomach of victims in a short lapse of time [81]. *G. vermiculophylla* is a source of different types of prostaglandins besides PGE₂, such as PGA₂, 15-keto-derivatives of prostaglandins, as well as other eicosanoids [82], whereas the congeneric species *G. asiatica* produces only 15-keto-PGE₂ [83]. *G. vermiculophylla* uses PGA₂, PGE₂, 15-keto-PGE₂ and other eicosanoids as wounding-activated chemical defense molecules (Table 2) [66], and recently a COX gene producing PGF₂α was cloned from this alga and heterologously expressed [84].

Other evidence of prostaglandins as defense molecules in red algae is the fact that gametophytes of the alga *Chondrus crispus* Stackhouse, 1797, when challenged with pathogens, metabolize C20 and C18 PUFAs not only into the corresponding hydroperoxides and derivatives, but also into molecules with mass fragmentation patterns very similar to prostaglandin B₁ and B₂ [85]. Furthermore, when the crude extract of this alga was treated with 50–100 µM methyl jasmonate for 6 h, PGA₂ and 15-keto-PGE₂ were identified [86].

### 3.4.2. Brown Macroalgae

Much less is known about the presence of prostaglandins in brown algae, and most studies have mainly focused on the brown algal kelp *Laminaria digitata*. Ritter et al. [19] showed that this brown alga uses the generation of oxylipins as a protective mechanism against stress conditions induced by an excess in copper (Table 2). Indeed, high concentrations of copper led to oxygen reactive species (ROS) accumulation in *L. digitata* cells, and consequently to a cascade of cellular responses. One of these responses was a significant release of PUFAs after 24 h of treatment, followed by the generation of oxylipins. Among complex oxylipins, also PGE₁ and PGD₁, deriving from ETrA and PGJ₂, PGA₂, 15-keto-PGE₂ and PGB₂, deriving from ARA were identified for the first time in brown algae [19]. Successively, the same authors showed that PGA₂ does not simply modulate but also triggers an oxidative response in *L. digitata* that, differently from the response induced by other molecules like methyljasmonate and lipopolysaccharides, occurs in seconds after treatment and in a dose-response-like manner. The authors hypothesized that PGA₂ can activate the generation of two different sources of ROS that can be used by the brown alga as defense molecules as in other marine organisms [68] (Figure 7).

![Figure 7. Brown algae prostaglandins: only *Laminaria digitata* has been studied for prostaglandins content. For details, refer to the text.](image)

### 3.5. Microalgae

PGs were discovered for the first time in diatoms, phytoplanktonic marine microalgae, only in 2017 [23]. Diatoms are a rich source of polyunsaturated fatty acids (PUFA), that, in some...
species, are precursors of polyunsaturated aldehydes (PUAs), i.e., oxylipins with pro-apoptotic and anti-proliferative activity, with a defensive role against predator (copepods) grazing [87].

Di Dato et al. [23] explored the presence of PGs in some diatom species, i.e. *Skeletonema marinoi* Sarno & Zingone, 2005 (Figure 8a) (two different strains, FE7 and FE60) and *Thalassiosira rotula* Meunier, 1910 (Figure 8b) (Valeria Di Dato, Roberta Barbarinaldi, Alberto Amato, Federica Di Costanzo, Carolina Fontanarosa, Anna Perna, Angela Amoresano, Francesco Esposito, Adele Cutignano, Adrianna Ianora, Giovanna Romano. Variation in prostaglandin metabolism during growth of the diatom *Thalassiosira rotula*. *Sci Rep*, under review), identifying in their transcriptome genes involved in PGs biosynthesis, with some differences between the two species.

![Figure 8. Microalgae prostaglandins. (a) *Skeletonema marinoi* (A. Ianora laboratory clones name FE7 and FE60); (b) *Thalassiosira rotula*; (c) *Euglena gracilis*; (d) *Microcystis aeruginosa*. For details, refer to the text.](image)

More specifically, whereas cyclooxygenase-1 (COX-1) and microsomal prostaglandin E synthase 1 (mPTGES) were found in both species; prostaglandin H2 D-isomerase (PTGDS) was found only in *S. marinoi*, while prostaglandin F synthase (PTGFS) was only detectable in *T. rotula*. The authors demonstrated the functioning of the pathway by measuring enzyme expression and molecule production by quantitative real time PCR (qPCR) and liquid chromatography/mass spectrometry (LC/MS) analysis, respectively. Interestingly, a wide set of PGs was revealed with representative molecules of each of the three series. In addition, a differential expression and concentration of molecules was reported among different species and strains of the same species, during different phases of growth and nutrient conditions [23]. However, the absence of PTGDS in *T. rotula* and of PTGFS in *S. marinoi* could be considered as a “potential absence.” Indeed, the lack of a transcript in a transcriptome annotation can be due to a technical shortcoming and a limitation of the sequencing technology used, as in the case of very low expression levels of a target gene, that may fall under the detection limit.
It is interesting to note that, although the PGs pathway has been experimentally confirmed only in two diatom species, in silico analysis of transcriptomes from different species in different growth conditions, suggests the presence of PGs in many other diatom species [23].

Prostaglandins were identified also in the unicellular green alga Euglena gracilis G. A. Klebs, 1883 (Figure 8c), in which PGE$_2$ and PGF$_2\alpha$ were found at levels three times higher in cells grown in the dark than those grown in the light [88].

The presence of PGA, PGE, and PGF series and their esters have also been documented in the cyanobacteria of the taxa Oscillatoria and Microcystidaceae [89]. Indeed, PGF$_2\alpha$ was identified in Microcystis aeruginosa (Kützing) Kützing, 1846 [90] (Figure 8d).

Currently, to the best of our knowledge, no other marine microalga has been explored for the presence of PGs, and their role in diatoms is still under investigation. Di Dato and co-authors hypothesized that they can be used by diatoms for intercellular signaling and communication [23], in agreement with the role of these molecules in other organisms.

Microorganisms, and in particular microalgae such as diatoms, could represent a potential source of bioactive PGs, as alternative to their chemical synthesis to produce adequate amounts for pharmacological purposes as anti-inflammatory compounds. The biotechnological production of PGs from microalgae may also be convenient due to the natural presence of the full PGs pathway and the possibility to easily grow microalgae on a large scale in bioreactors under controlled culture conditions.

4. Marine Cyclopentenone Prostaglandins

Cyclopentenone prostaglandins are a sub-group of PGs characterized by the presence of a cyclopentenone moiety (CP) with a $\alpha,\beta$-unsaturated ketone group in their cyclopentane ring. Their chemical reactivity is responsible for their anti-inflammatory, anti-tumoral and anti-viral activities [91], and the presence of the CP fragment in molecules with anticancer activity, can add more potency to these molecules. For instance, methyl-jasmonate increases its strength of action as an anti-tumor agent when a CP group is inserted in the molecule [92].

The group of cyclopentenone prostaglandins (CPPGs) includes canonical PGs of the A and J series, clavulones, and punaglandins.

Differently from the conventional PGs, that require receptor interaction to trigger their signal, cyclopentenone prostaglandins are actively transported inside the cells [91], where the CP group can interact with a wide variety of target molecules [92] including nuclear factors such as the heat shock protein 70 (HSP70) transcription factor, cyclin-dependent protein kinase (CDK), and NF-kB [35] and still not well defined mitochondrial factors [92].

4.1. Clavulones and Related Molecules

Clavulones (Figure 9) are acetoxy derivatives of PGA [91] characterized by a cyclopentenone fragment, a 12-$S$ acetoxy function and two chains of different length: the $\alpha$- and the $\omega$-chain with respectively seven and eight carbon atoms [93]. These are anti-tumor marine prostanoids isolated from the soft coral Clavularia viridis Quoy & Gaimard, 1833, a single Clavularia genus that inhabits Okinawa bay in Japan [44,94,95].

Clavulones exists in three isoforms, I, II, and III and two stereoisomers at the C-4 and C-12 positions. These molecules possess a significant anti-inflammatory effect at a concentration of 30 $\mu$g/mL in a fertilized chicken egg assay (Table 1) [44,95]. The effects of clavulones on the growth of human cancer cells were first studied using clavulone I, the form that is more abundant in C. viridis.

At concentration of 4.0 $\mu$M there was an impairment of DNA synthesis in human HL-60 leukemia cells after 1 h incubation, causing irreversible cytotoxic changes after 3 h of exposition [45]. In a more recent study, the anti-cancer activity of clavulone II on HL-60 cells has been deeply studied [46] revealing that low concentrations of clavulone II induce anti-proliferative effects by inducing the down-regulation of cyclin D1 with consequent arrest of the cell cycle in G1. On the contrary, higher concentrations of clavulone II induces apoptosis through the disruption of mitochondrial membrane potential and the
activation of caspase-9, -8, and -3 and of B-cell lymphoma 2 (Bcl2)-family proteins (Table 1) [46]. It was suggested that corals might use clavulones as repellent and toxic substances against other marine organisms (Table 2) [45].

Clavulones, similarly to PGAs, also possess antiviral activity. In particular, clavulone II inhibits replication of the vesicular stomatitis virus (VSV) in infected mouse L929 fibroblasts, by blocking the transcription of viral RNA, and consequently the viral protein (Table 1) [47]. Interestingly, both the anti-proliferative and antiviral activities of clavulones are stronger than those of PGAs [47].

Other than clavulone I, II, and III, from the same stolonifer coral, 20-acetoxi-claviridenone b and 20-acetoxi-claviridenone c were discovered [96]. In addition to these, also four halogenated analogues, called chlorovulones I-IV were identified and, among these, chlorovulone I was shown to have anti-proliferative and cytotoxic activities (Table 1) [48]. The structure of an epoxy prostanoid with anti-proliferative activity was also identified in the same soft coral [49] together with bromovulone I and iodovulone I. Both had anti-proliferative and cytotoxic activities even though slightly lower than those of chlorovulone I [50]. All these molecules showed a stronger anti-tumor activity against HL-60 cells in vitro with respect to clavulone I (Table 1) [48–50].

More recently, seven new prostanoids were identified from the same soft coral: 4-deacetoxyl-12-O-deacetylclavulone I, 4-deacetoxyl-12-O-deacetylclavulone II, bromovulone II, iodovulone II, 4-deacetoxyl-12-O-deacetylclavulone III, bromovulone III, and iodovulone III. These molecules showed in vitro cytotoxic activity against human prostate carcinoma (PC-3) and colon adenocarcinoma (HT-29) cells and, among these, bromovulone III showed the highest anti-tumor activity, together with chlorovulone II and III, used as standard, that exhibited a slightly lower activity (Table 1) [51].

Through an assay-guided fractionation of a dichloromethane (CH$_2$Cl$_2$) extract of C. viridis, three new cytotoxic molecules were isolated: claviridenone E, claviridenone F, and claviridenone G. In particular, claviridenone F showed a significant cytotoxicity against human lung adenocarcinoma (A549), HT-29, and mouse lymphocytic leukemia cells (P-388), while claviridenone G exhibited a high cytotoxic activity only against A549 (Table 1) [52]. In addition to these molecules, there are clavulone-related oxylipins from C. viridis, named clavirins I and II, for which it was proposed a
derivation from clavulone III and I, respectively, having growth-inhibitory activity against human cervix carcinoma cell line (HeLa S3) (Table 1) [53].

Other clavulone-related molecules that have been discovered are tricycloclavulone and clavubicyclone that may be derived from cycloaddition and electrocyclization of clavulone III, respectively. The latter molecule showed a moderate growth-inhibition activity against breast carcinoma (MCF-7) and ovarian carcinoma cells (OVCAR-3) in vitro (Table 1) [54]. Preclavulone lactone I and II and two minor chemical congeners, 17,18-dehydroclavulone I and clavulolactone I, were also isolated and characterized from C. viridis. Among these, 17,18-dehydroclavulone I has a (14Z,17Z)-double bond in the ω side chain, and this suggests that, differently from the other clavulones, it can derive from EPA instead of ARA [97].

Although there are structural similarities between prostaglandins and clavulones, the latter are not generated by a variant of the endoperoxide pathway, but from the lipoxygenase pathway by which arachidonic acid is converted into 8-(R)HPETE and then to preclavulone A [98]. Preclavulone A was identified also in an unrelated Caribbean coral, Pseudoplexaura porosa Houttuyn, 1772, suggesting that this molecule is widespread in corals [99]. In another study, the same authors isolated and defined the structures of 15 new halogenated iodo-, bromo-, and chlorovulones in C. viridis as minor constituents [100], but overall about 50 congeners of clavulones were identified in this soft coral [101].

4.2. Punaglandins

These molecules (Figure 10), structurally related to clavulones, were isolated in the Hawaiian octocoral Telesto riisei Duchassaing & Michelotti, 1860 [102].

The lack of symbiotic algae suggests that T. riisei is the source of these prostaglandins [103]. A total of 19 punaglandins were obtained from this octocoral, which also included acetate and epoxide versions of the four canonical punaglandins [104]. Punaglandins 3 and 4 formally results from elimination of acetic acid from punaglandins 1 and 2 respectively, and possess a cross-conjugated dienone structure [105]. They are halogenated derivatives of PGA [91] characterized by various oxygenations at C -5, -6, -7, and -12 and a 10-chloro-9-cyclopentenone function with a 5S, 6S, 12R stereochemistry [102].

At the moment of their discovery, there was great interest in the study of punaglandins, because of their anti-inflammatory and potent antitumor activities [104]. Indeed, these molecules, and in particular punaglandin 3, was shown to inhibit L1210 leukemia cell proliferation (IC$_{50}$ = 0.04 µM).
with an activity 15-fold higher compared to the corresponding clavulone [55]. This cytotoxic activity is approximately equal to the one of vincristine and doxorubicin that are among the most effective anticancer molecules used today [103].

5. Marine Thromboxane

Thromboxanes (TXs) are closely related to PGs that bind specific receptors, called thromboxane receptors (TP) and act as strong promoters of platelet aggregation and vaso- and broncho-constriction in mammals [106]. They are labile and biologically active molecules deriving from arachidonic acid in the cyclooxygenase pathway in human platelets. Thromboxane A2 (TXA2) has a short half-life (30 s in human blood) being rapidly converted to a stable B form (TXB2), which is used as a marker for the presence of TXA2 [69].

Other than in mammals, the presence of TXs is documented also in marine organisms. TXB2, along with prostaglandins, has been reported in aqueous homogenates of the mollusc A. californica J. G. Cooper, 1863 (Figure 4a) [74] using radioimmunoassay. In the marine bivalve M. edulis Linnaeus, 1758 (Figure 4a), arachidonic acid metabolism, in addition to PGs, leads to the production of TXs in the gills, mantle, and adductor tissues [107]. In the polychaetae Arenicola marina Linnaeus, 1758 small amounts of TXB2 are detectable in the digestive and reproductive tracts [107].

Different species of fish also produce TXs [69]. In the plasma of the elasmobranch Dasyatis sabina Lesueur, 1824 (Figure 5b), the presence of an immunoreactive TXB2 (iTXB2) has been detected at concentrations of 0.57 ± 0.03 ng/mL. The level of iTXB2 increased to 3.0 ± 0.27 ng/mL when the plasma clots, but decreased to 1.5 ± 0.17 ng/mL in the presence of indomethacin, a cyclooxygenase inhibitor. These findings suggest that TXA2, the active thromboxane form, may be involved in blood clotting and may be generated by a cyclooxygenase-like enzyme as in mammals (Table 2) [69]. The binding of agonist (radiolabeled [125I]-BOP) and antagonist (L-657925 and L-657926) ligands of mammalian TP receptors to those of D. sabina, also demonstrates the similarity between this elasmobranch and mammalian TP receptors [69]. Three different species of shark (Figure 5b) (Chiloscyllium griseum Müller & Henle, 1838, Carcharhinus plumbeus Nardo, 1827 and Carcharhinus melanopterus Quoy & Gaimard, 1824) were also shown to produce TXB2 as a major product of arachidonic acid metabolism suggesting that TXB2 may be a biologically active prostanoid in these species [70].

Rowley et al. [78] tested the ability of leucocytes extracted from the blood of the dogfish Scyliorhinus canicula (Figure 5b) to produce and release PGs and TXs during their degranulation induced by the calcium ionophore A23187. While PGF2α, PGE2, and PGD2 levels were always high after the stimulus, the levels of TXB2 were low and detectable in the supernatant only 5 min after the start of the stimulus, with levels increasing after 10 and 15 min [78].

Another direct evidence of the generation of TXB2 in fish was demonstrated by the ability of washed whole blood cells from a variety of fishes of the Arabian Gulf to produce prostanoids from exogenous 14C-arachidonic acid in vitro [70]. In addition, rainbow trout thrombocytes, clotting cells similar to mammalian platelets, were shown to convert arachidonic acid mainly to TXB2 [108,109]. These findings again suggest a role also for TXB2, in rainbow trout as a vasodilator (Table 2), while in mammals TXB2 has no significant biological activity [70]. However, not all fish thrombocytes have the ability to produce thromboxane, possibly suggesting that these molecules are not essential for thrombocyte aggregation in certain species [110].

6. Conclusions

Prostaglandins and their derivatives, although first identified in terrestrial organisms, are also widespread in the marine environment testifying the great importance of these molecules. Nevertheless, the eco-physiological role of marine PGs remains mostly unclear because of contrasting and often old data available in the literature, although it has been suggested that they have a possible role as defensive molecules against predators.
Interestingly, many marine organisms have been shown to produce classical PGs along with new derivatives that are not found in terrestrial animals, e.g., corals that are able to produce punaglandins and clavulones, which are specific of the marine environment and have shown potent pharmacological activity against inflammation, tumors, and viruses. These findings, together with the discovery of PGs in unicellular eukaryotic microalgae, provides new stimuli to pursue the search for new marine PG-derived molecules with anti-inflammatory activity.

Author Contributions: Conceptualization, V.D.D., G.R. and F.D.C.; methodology, V.D.D., G.R. and F.D.C.; resources, V.D.D., G.R. and F.D.C.; writing—original draft preparation, F.D.C., G.R. and V.D.D.; writing—review and editing, F.D.C., V.D.D., G.R. and A.I.; visualization, G.R. and A.I.; supervision, V.D.D., G.R. and A.I.; project administration, G.R.; funding acquisition, G.R.

Funding: This research was funded by Ministero dell’ambiente e della tutela del territorio e del mare, Italia, project name: “Genomics for a Blue Economy,” grant number PGR00765.

Acknowledgments: We thank Adele Cutignano (Institute of Biomolecular Chemistry-National Research Council of Italy) for her help in drawing the molecules.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References
1. Cheung, R.C.F.; Ng, T.B.; Wong, J.H.; Chen, Y.; Chan, W.Y. Marine natural products with anti-inflammatory activity. *Appl. Microbiol. Biotechnol.* 2016, 100, 1645–1666. [CrossRef] [PubMed]
2. Mora, C.; Tittensor, D.P.; Adl, S.; Simpson, A.G.B.; Worm, B. How many species are there on Earth and in the ocean? *PloS Biol.* 2011, 9, e1001127. [CrossRef] [PubMed]
3. Buckley, C.D.; Gilroy, D.W.; Serhan, C.N.; Stockinger, B.; Tak, P.P. The resolution of inflammation. *Nat. Rev. Immunol.* 2013, 13, 59–66. [CrossRef] [PubMed]
4. Fullerton, J.N.; Gilroy, D.W. Resolution of inflammation: A new therapeutic frontier. *Nat. Rev. Drug Discov.* 2016, 15, 551–567. [CrossRef] [PubMed]
5. Gilroy, D.; De Maeyer, R. New insights into the resolution of inflammation. *Semin. Immunol.* 2015, 27, 161–168. [CrossRef] [PubMed]
6. Headland, S.E.; Norling, L.V. The resolution of inflammation: Principles and challenges. *Semin. Immunol.* 2015, 27, 149–160. [CrossRef] [PubMed]
7. Ortega-Gómez, A.; Perretti, M.; Soehnlein, O. Resolution of inflammation: An integrated view. *EMBO Mol. Med.* 2013, 5, 661–674. [CrossRef] [PubMed]
8. Serhan, C.N.; Chiang, N.; Dalli, J.; Levy, B.D. Lipid mediators in the resolution of inflammation. *Cold Spring Harb. Perspect. Biol.* 2014, 7, a016311. [CrossRef] [PubMed]
9. Rajakariar, R.; Yaqoob, M.M.; Gilroy, D.W. COX-2 in inflammation and resolution. *Mol. Interv.* 2006, 6, 199–207. [CrossRef] [PubMed]
10. Murata, T.; Maehara, T. Discovery of anti-inflammatory role of prostaglandin D2. *J. Vet. Med. Sci.* 2016, 78, 1643–1647. [CrossRef] [PubMed]
11. Euler, U.S.v. Zur Kenntnis der pharmakologischen Wirkungen von Nativsekreten und Extrakten männlicher accessorischer Geschlechtsdrüsen. *Arch. Exp. Pathol. Pharmacol.* 1934, 175, 78–84. [CrossRef]
12. Coldblatt, M.W. Properties of human seminal plasma. *J. Physiol.* 1935, 84, 208–218. [CrossRef] [PubMed]
13. Wolfe, L.S. Eicosanoids: Prostaglandins, thromboxanes, leukotrienes, and other derivatives of carbon-20 unsaturated fatty acids. *J. Neurochem.* 1982, 38, 1–14. [CrossRef] [PubMed]
14. Piper, P.J. Introduction to the biosynthesis and metabolism of prostaglandins. *Postgrad. Med. J.* 1977, 53, 643–646. [CrossRef] [PubMed]
15. Bhakuni, D.S.; Rawat, D.S. *Bioactive Marine Natural Products*; Springer: New York, NY, USA; Anamaya: New Delhi, India, 2005; ISBN 978-1-4020-3472-5.
16. Nomura, T.; Ogata, H. Distribution of prostaglandins in the animal kingdom. *Biochim. Biophys. Acta* 1976, 431, 127–131. [PubMed]
17. Rowley, A.F.; Vogan, C.L.; Taylor, G.W.; Clare, A.S. Prostaglandins in non-insectan invertebrates: Recent insights and unsolved problems. *J. Exp. Biol.* 2005, 208, 3–14. [CrossRef] [PubMed]
18. Sajiki, J.; Kakimi, H. Identification of eicosanoids in the red algae, *Gruclaria asiatica*, using high-performance liquid chromatography and electrospray ionization mass spectrometry. *J. Chromatogr. A* **1998**, *795*, 227–237. [CrossRef]

19. Ritter, A.; Goulitzer, S.; Salátin, J.-P.; Tonon, T.; Correa, J.A.; Potin, P. Copper stress induces biosynthesis of octadecanoid and eicosanoid oxygenated derivatives in the brown algal kelp *Laminaria digitata*. *New Phytol.* **2008**, *180*, 809–821. [CrossRef]

20. Groenewald, E.G.; van der Westhuizen, A.J. Prostaglandins and related substances in plants. *Bot. Rev.* **1997**, *63*, 199–220. [CrossRef]

21. Ruggeri, B.; Thoroughgood, C. Prostaglandins in aquatic fauna: A comprehensive review. *Mar. Ecol. Prog. Ser.* **1985**, *23*, 301–306. [CrossRef]

22. Carté, B.K. Biomedical potential of marine natural products. Marine organisms are yielding novel molecules for use in basic research and medical applications. *BioScience* **1996**, *46*, 271–286.

23. Di Dato, V.; Orefice, I.; Amato, A.; Fontanarosa, C.; Amoresano, A.; Cutignano, A.; Ianora, A.; Romano, G. Animal-like prostaglandins in marine microalgae. *ISME J.* **2017**, *11*, 1722–1726. [CrossRef] [PubMed]

24. Nakanishi, M.; Rosenberg, D.W. Multifaceted roles of PGE2 in inflammation and cancer. *Semin. Immunopathol.* **2013**, *35*, 123–137. [CrossRef] [PubMed]

25. Lands, W.E.M. The biosynthesis and metabolism of prostaglandins. *Annu. Rev. Physiol.* **1979**, *41*, 633–652. [CrossRef] [PubMed]

26. Bos, C.L.; Richel, D.J.; Ritsema, T.; Peppelenbosch, M.P.; Versteeg, H.H. Prostanoids and prostanoid receptors in signal transduction. *Int. J. Biochem. Cell Biol.* **2004**, *36*, 1187–1205. [CrossRef] [PubMed]

27. Funk, C.D. Prostaglandins and leukotrienes: Advances in eicosanoid biology. *Science* **2001**, *294*, 1871–1875. [CrossRef] [PubMed]

28. Hansen, H.S. 15-hydroxyprostaglandin dehydrogenase. A review. *Prostaglandins* **1976**, *12*, 647–679. [CrossRef]

29. Wang, D.; DuBois, R.N. Prostaglandins and cancer. *Gut* **2006**, *55*, 115–122. [CrossRef]

30. Jakobsson, P.J.; Thorén, S.; Morgenstern, R.; Samuelsson, B. Identification of human prostaglandin E synthase: A microsomal, glutathione-dependent, inducible enzyme, constituting a potential novel drug target. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 7220–7225. [CrossRef]

31. Sykes, L.; MacIntyre, D.A.; Teoh, T.G.; Bennett, P.R. Anti-inflammatory prostaglandins for the prevention of preterm labour. *Reproduction* **2014**, *148*, R29–R40. [CrossRef]

32. Basu, S. Novel cyclooxygenase-catalyzed bioactive prostaglandin F2alpha from physiology to new principles in inflammation. *Med. Res. Rev.* **2007**, *27*, 435–468. [CrossRef] [PubMed]

33. Ricciotti, E.; FitzGerald, G.A. Prostaglandins and inflammation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 986–1000. [CrossRef] [PubMed]

34. Watanabe, T.; Nakao, A.; Emerling, D.; Hashimoto, Y.; Tsukamoto, K.; Horie, Y.; Kinoshita, M.; Kurokawa, K. Prostaglandin F2alpha enhances tyrosine phosphorylation and DNA synthesis through phospholipase C-coupled receptor via Ca(2+) dependent intracellular pathway in NIH-3T3 cells. *J. Biol. Chem.* **1994**, *269*, 17619–17625. [PubMed]

35. Straus, D.S.; Glass, C.K. Cyclopentenone prostaglandins: New insights on biological activities and cellular targets. *Med. Res. Rev.* **2001**, *21*, 185–210. [CrossRef] [PubMed]

36. Brown, J.A.; Bucknall, R.M. Antidiuretic and cardiovascular actions of prostaglandin E2 in the rainbow trout *Salmo gairdneri*. *Gen. Comp. Endocrinol.* **1986**, *61*, 330–337. [CrossRef]

37. Di Marzo, V.; Cimino, G.; Crispino, A.; Minardi, C.; Sodano, G.; Spinella, A. A novel multifunctional metabolic pathway in a marine mollusc leads to unprecedented prostaglandin derivatives (prostaglandin 1,15-lactones). *Biochem. J.* **1991**, *273* (Pt 3), 593–600. [CrossRef]

38. Weinheimer, A.J.; Spraggins, R.L. The occurrence of two new prostaglandin derivatives (15-epi-PGA2 and its acetate, methyl ester) in the gorgonian *Plexaura homomalla* chemistry of coelenterates. XV. *Tetrahedron Lett.* **1969**, *59*, 5185–5188. [CrossRef]

39. Light, R.J.; Samuelsson, B. Identification of prostaglandins in the gorgonian, *Plexaura homomalla*. *Eur. J. Biochem.* **1972**, *28*, 232–240. [CrossRef]

40. Schneider, W.P.; Hamilton, R.D.; Rhuland, L.E. Occurrence of esters of (15S)-prostaglandin A2 and E2 in coral. *J. Am. Chem. Soc.* **1972**, *94*, 2122–2123. [CrossRef]
53. Iwashima, M.; Okamoto, K.; Iguchi, K. Clavirins, a new type of marine oxylipins with growth-inhibitory activity.

54. Iwashima, M.; Terada, I.; Okamoto, K.; Iguchi, K. Tricycloclavulone and clavubicyclone, novel prostanoid-related marine oxylipins, isolated from the Okinawan Soft Coral, Clavularia viridis.

55. Baker, B.J.; Okuda, R.K.; Yu, P.T.K.; Scheuer, P.J. Punaglandins: Halogenated antitumor eicosanoids from the Formosan Soft Coral, Clavularia violacea.

56. Komoda, Y.; Kanayasu, T.; Ishikawa, M. Prostaglandin F 2 alpha from the Japanese coastal gorgonian, Clavularia japonica.

57. Carmely, S.; Kashman, Y.; Loya, Y.; Benayahu, Y. New prostaglandin (PGF) derivatives from the Soft Coral, Clavularia viridis.

58. Varvas, K.; Järving, I.; Koljak, R.; Vahemets, A.; Pehk, T.; Mührisepp, A.-M.; Lille, Ü.; Samel, N. The biosynthesis of prostaglandins in the White Sea Soft Coral Gersemia fruticosa: Formation of optically active 13-keto-PGF2, 15-keto-PGF2α and 15-keto-PGF2β from arachidonic acid.

59. Järving, I.; Kuznetsov, D.; Shpursky, R.; Sepp, T.; Yilmaz, F.; Samel, N. In vitro biosynthesis of prostaglandins in the White Sea Soft Coral Gersemia fruticosa: Formation of optically active PGD2, PGE2, PGF2α and 15-keto-PGF2α from arachidonic acid.

60. Christ, E.J.; Van Dorp, D.A. Comparative aspects of prostaglandin biosynthesis in animal tissues. Biochim. Biophys. Acta (BBA)—Lipids Lipid Metab. 1972, 270, 537–545.

61. Bayer, F.; Weinheimer, A. Prostaglandins from Plexaura homomalla: Ecology, Utilization and Conservation of a Major Marine Resource. A Symposium; Studies in Tropical Oceanography; University of Miami Press on Behalf of the Upjohn Co.: Coral Gables, FL, USA, 1974.

62. Gerhart, D.J. Prostaglandin A 2: An agent of chemical defense in the Caribbean gorgonian Plexaura homomalla. Mar. Ecol. Prog. Ser. 1984, 19, 181–187. [CrossRef]

63. Reina, E.; Ramos, F.A.; Castellanos, L.; Aragón, M.; Osmpina, L.F. Anti-inflammatory R-prostaglandins from Caribbean Colombian Soft Coral Plexaura homomalla. J. Pharm. Pharmacol. 2013, 65, 1643–1652. [CrossRef] [PubMed]

64. Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. Absolute stereochemistry of new prostanoids clavulone I, II and III, from Clavularia viridis Quoy and Gaimard. Tetrahedron Lett. 1983, 24, 1549–1552. [CrossRef] [PubMed]

65. Honda, A.; Yamamoto, Y.; Mori, Y.; Yamada, Y.; Kikuchi, H. Antileukemic effect of coral-prostanoids clavulones from the stolonifer Clavularia viridis on human myeloid leukemia (HL-60) cells. Biochem. Biophys. Res. Commun. 1985, 130, 515–523. [CrossRef]

66. Huang, Y.-C.; Guh, J.-H.; Shen, Y.-C.; Teng, C.-M. Investigation of anticancer mechanism of clavulone II, a coral cyclopentenone prostaglandin analog, in human acute promyelocytic leukemia. J. Biomed. Sci. 2005, 12, 335–345. [CrossRef] [PubMed]

67. Bader, T.; Yamada, Y.; Ankel, H. Antiviral activity of the prostanoïd clavulone II against vesicular stomatitis virus. Antivir. Res. 1991, 16, 341–355. [CrossRef]

68. Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. Chlorovulones, new halogenated marine prostanoids with an antitumor activity from the stolonifer Clavularia viridis Quoy and Gaimard. Tetrahedron Lett. 1985, 26, 5787–5790. [CrossRef]

69. Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y. A new marine epoxy prostanoïd with an antiproliferative activity from the stolonifer Clavularia viridis Quoy and Gaimard. Chem. Pharm. Bull. 1987, 35, 4375–4376. [CrossRef] [PubMed]

70. Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. Bromovulone I and iodovulone I, unprecedented brominated and iodinated marine prostanoids with antitumour activity isolated from the Japanese stolonifer Clavularia viridis Quoy and Gaimard. J. Chem. Soc. Chem. Commun. 1986, 981–982. [CrossRef]

71. Shen, Y.-C.; Cheng, Y.-B.; Lin, Y.-C.; Guh, J.-H.; Teng, C.-M.; Ko, C.-L. New prostanoids with cytotoxic activity from Taiwanese octocoral Clavularia viridis. J. Nat. Prod. 2004, 67, 542–546. [CrossRef]

72. Duh, C.-Y.; El-Gamal, A.A.H.; Chu, C.-J.; Wang, S.-K.; Dai, C.-F. New cytotoxic constituents from the Formosan Soft Coral Clavularia viridis and Clavularia violacea. J. Nat. Prod. 2002, 65, 1535–1539. [CrossRef]

73. Iwashima, M.; Okamoto, K.; Iguchi, K. Clavirins, a new type of marine oxylipins with growth-inhibitory activity from the Okinawan soft coral, Clavularia viridis. Tetrahedron Lett. 1990, 24, 567–570. [CrossRef]

74. Iwashima, M.; Terada, I.; Okamoto, K.; Iguchi, K. Tricycloclavulone and clavubicyclone, novel prostanoid-related marine oxylipins, isolated from the Okinawan Soft Coral Clavularia viridis. J. Org. Chem. 2002, 67, 2977–2981. [CrossRef] [PubMed]

75. Baker, B.J.; Okuda, R.K.; Yu, P.T.K.; Scheuer, P.J. Prostaglandins: Halogenated antitumor eicosanoids from the octocoral Telescopiidae. J. Am. Chem. Soc. 1985, 107, 2976–2977. [CrossRef] [PubMed]

76. Komoda, Y.; Kanayasu, T.; Ishikawa, M. Prostaglandin F 2 alpha from the Japanese coastal gorgonian, Euplexaura erecta. Chem. Pharm. Bull. 1979, 27, 2491–2494. [CrossRef] [PubMed]

77. Carmely, S.; Kashman, Y.; Loya, Y.; Benayahu, Y. New prostaglandin (PGF) derivatives from the Soft Coral, Tetrahedron Lett. 1980, 21, 875–878. [CrossRef]

78. Varvas, K.; Järving, I.; Koljak, R.; Vahemets, A.; Pehk, T.; Mührisepp, A.-M.; Lille, Ü.; Samel, N. In vitro biosynthesis of prostaglandins in the White Sea Soft Coral Gersemia fruticosa: Formation of optically active PGD2, PGE2, PGF2α and 15-keto-PGF2α from arachidonic acid. Tetrahedron Lett. 1993, 34, 3643–3646. [CrossRef]

79. Järving, I.; Järving, I.; Kurk, R.; Brash, A.R.; Samel, N. On the evolutionary origin of cytochrome oxidase (COX) isozymes: Characterization of marine invertebrate COX genes points to independent duplication events in vertebrate and invertebrate lineages. J. Biol. Chem. 2004, 279, 13624–13633. [CrossRef] [PubMed]
61. Ogata, H.; Nomura, T.; Hata, M. Prostaglandin biosynthesis in the tissue homogenates of marine animals. NIPPON SUISAN GAKKAISHI 1978, 44, 1367–1370. [CrossRef]

62. Levine, L.; Kobayashi, T. Detection of compounds immunologically related to arachidonic acid transformation products in extracts of invertebrates. Prostaglandins Leukot. Med. 1983, 12, 357–369. [CrossRef]

63. Stanley-Samuelson, D.W. Physiological roles of prostaglandins and other eicosanoids in invertebrates. Biol. Bull. 1987, 173, 92–109. [CrossRef] [PubMed]

64. Tahara, D.; Yano, I. Maturation-related variations in prostaglandin and fatty acid content of ovary in the kuruma prawn (Marsupenaeus japonicus). Comp. Biochem. Physiol. Part A Mol. Integr. Physiol. 2004, 137, 631–637. [CrossRef] [PubMed]

65. Nomura, T.; Ogata, H.; Masao, I.T.O. Occurrence of prostaglandins in fish testis. Russ. J. Mar. Biol. 1973, 24, 138–144.

66. Nylund, G.M.; Weinberger, F.; Rempt, M.; Pohnert, G. Metabolomic Assessment of induced and activated products in extracts of invertebrates. Prostaglandins Leukot. Med. 2012, 92, 13–23. [CrossRef] [PubMed]

67. Cimino, G.; Crispino, A.; Di Marzo, V.; Spinella, A.; Sodano, G. Prostaglandin 1,15-lactones of the F series products in extracts of invertebrates. Prostaglandins Leukot. Med. 2012, 92, 13–23. [CrossRef] [PubMed]

68. Zambounis, A.; Gaquerel, E.; Strittmatter, M.; Salaün, J.P.; Potin, P.; Küpper, F.C. Prostaglandin A₂ triggers a strong oxidative burst in Laminaria: A novel defense inducer in brown algae? ALGAE 2012, 27, 21–32. [CrossRef]

69. Cabrera, D.M.; Janech, M.G.; Morinelli, T.A.; Miller, D.H. A thromboxane A(2) system in the Atlantic stingray, Dasyatis sabina. Gen. Comp. Endocrinol. 2003, 130, 157–164. [CrossRef]

70. Thomson, M.; al-Hassan, J.M.; al-Saleh, J.; Fayad, S.; Ali, M. Prostanoid synthesis in whole blood cells from fish of the Arabian Gulf. Comp. Biochem. Physiol. B Biochem. Mol. Biol. 1998, 119, 639–646. [CrossRef]

71. Freas, W.; Grollman, S. Uptake and binding of prostaglandins in a marine bivalve, Modiolus demissus. J. Exp. Zool. 1981, 216, 225–233. [CrossRef]

72. Hampson, A.J.; Rowley, A.F.; Barrow, S.E.; Steadman, R. Biosynthesis of eicosanoids by blood cells of the crab, Carcinus maenas. Biochim. Biophys. Acta 1992, 1124, 143–150. [CrossRef]

73. Korotchenko, O.D.; Mishchenko, T.Y.; Isay, S.V. Prostaglandins of Japan Sea invertebrates—I. The quantitation of group B prostaglandins in echinoderms. Comp. Biochem. Physiol. Part C Comp. Pharmacol. 1983, 74, 85–88. [CrossRef]

74. Gerwick, W.H.; Nagle, D.G.; Proteau, P.J. Oxylipins from marine invertebrates. In Marine Natural Products—Diversity and Biosynthesis; Scheuer, P.J., Ed.; Springer: Berlin/Heidelberg, Germany, 1993; Volume 167, pp. 117–180. ISBN 978-3-540-56513-0.

75. Ogata, H.; Nomura, T.; Hata, M. Prostaglandin biosynthesis in the tissue homogenates of marine animals. NIPPON SUISAN GAKKAISHI 1978, 44, 1367–1370. [CrossRef]

76. Goetz, F.W.; Duman, P.; Ranjan, M.; Herman, C.A. Prostaglandin F and E synthesis by specific tissue components of the brook trout (Salvelinus fontinalis) ovary. J. Exp. Zool. 1989, 250, 196–205. [CrossRef]

77. Anderson, A.A.; Fletcher, T.C.; Smith, G.M. Prostaglandin biosynthesis in the skin of the plaice Pleuronectes platessa L. Comp. Biochem. Physiol. C Comp. Pharmacol. 1981, 70, 195–199. [CrossRef]

78. Rowley, A.F.; Barrow, S.E.; Hunt, T.C. Preliminary studies on eicosanoid production by fish leucocytes, using GC-mass spectrometry. J. Fish Biol. 1987, 31, 107–111. [CrossRef]

79. Cagen, L.M.; Qureshi, Z.; Nishimura, H. Synthesis of prostaglandin E2 and prostaglandin F2α by toadfish red blood cells. Biochim. Biophys. Res. Commun. 1983, 110, 250–255. [CrossRef]

80. Oyama, T.; Ohta, K.; Fujii, T.; Okada, Y.; Sugimori, T. The occurrence of 15-keto-prostaglandins in the red alga Gracilaria verrucosa. Arch. Pharm. Res. 2010, 33, 1325–1329. [CrossRef]

81. Hsu, B.-Y.; Tsao, C.-Y.; Chiou, T.-K.; Hwang, P.-A.; Hwang, D.-F. HPLC determination for prostaglandins from seaweed. Food Control 2007, 18, 639–645. [CrossRef]

82. Imbs, A.B.; Lataisky, N.A.; Svetashev, V.I.; Skripotsova, A.V.; Le, T.T.; Pham, M.Q.; Nguyen, V.S.; Pham, L.Q. Distribution of polyunsaturated fatty acids in red algae of the genus Gracilaria. Russ. J. Mar. Biol. 2012, 38, 339–345. [CrossRef]

83. De Almeida, C.L.F.; Falcão, H.d.S.; Lima, G.R.d.M.; Montenegro, C.d.A.; Lira, N.S.; de Athayde-Filho, P.F.; Rodrigues, L.C.; de Souza, M.d.F.V.; Barbosa-Filho, J.M.; Batista, L.M. Bioactivities from marine algae of the genus Gracilaria. Int. J. Mol. Sci. 2011, 12, 4550–4573. [CrossRef]
84. Kanamoto, H.; Takemura, M.; Ohyama, K. Identification of a cyclooxygenase gene from the red alga Gracilaria vermiculophylla and bioconversion of arachidonic acid to PGF(2α) in engineered Escherichia coli. Appl. Microbiol. Biotechnol. 2011, 91, 1121–1129. [CrossRef] [PubMed]

85. Bouarab, K.; Adas, F.; Gaquered, E.; Kloareg, B.; Salatín, J.-P.; Potin, P. The innate immunity of a marine red alga involves oxylipins from both the eicosanoid and octadecanoid pathways. Plant Physiol. 2004, 135, 1838–1848. [CrossRef] [PubMed]

86. Andreou, A.; Brodhun, F.; Feusnner, I. Biosynthesis of oxylipins in non-mammals. Prog. Lipid Res. 2009, 48, 148–170. [CrossRef] [PubMed]

87. Ianora, A.; Miralto, A. Toxigenic effects of diatoms on grazers, phytoplankton and other microbes: A review. Ecotoxicology 2010, 19, 493–511. [CrossRef] [PubMed]

88. Levine, L.; Sneiders, A.; Kobayashi, T.; Schi

89. Kafanova, T.V.; Busarova, N.G.; Zveda, T.V.; Zvyagintseva, T.Y. Fatty acids and prostaglandins of thermal organisms. In Marine Drugs 2019, 17, 428.

90. Krüger, G.H.J.; Groenewald, E.G.; de Wet, H.; Botes, P.J. The occurrence of prostaglandin F2α in procaryotic organisms. S. Afr. J. Bot. 1990, 56, 150–153. [CrossRef]

91. Narumiya, S.; Fukushima, M. Cyclopentenone prostaglandins: Anti-proliferative and anti-viral actions and their molecular mechanism. In Eicosanoids and Other Bioactive Lipids in Cancer and Radiation Injury: Proceedings of the 1st International Conference 11–14 October 1989, Detroit, MI, USA; Honn, K.V., Marnett, L.J., Nigam, S., Walden, T.L., Eds.; Developments in Oncology; Springer: Boston, MA, USA, 1991; pp. 439–448. ISBN 978-1-4615-3874-5.

92. Conti, M. Cyclopentenone: A special moiety for anticancer drug design. Anticancer Drugs 2006, 17, 1017–1022. [CrossRef]

93. Lis, L.G.; Zheldakova, T.A. New marine prostanoids, clavulones, halogenovulones, and punaglandins. Chem. Nat. Compd. 1993, 29, 259–274. [CrossRef]

94. Imbs, A.B. Prostaglandins and oxylipins of corals. Russ. J. Mar. Biol. 2011, 37, 325–334. [CrossRef]

95. Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. Clavulones, new type of prostanoids from the stolonifer Clavularia viridis Quoy and Gaimard. Tetrahedron Lett. 1982, 23, 5171–5174. [CrossRef]

96. Tagawa, I.; Kobayashi, M.; Yasuzawa, T.; Son, B.W.; Yoshihara, M.; Kyogoku, Y. New prostanooids from Soft Coral. Tetrahedron 1985, 41, 995–1005. [CrossRef]

97. Iwashima, M.; Okamoto, K.; Konno, F.; Iguchi, K. New marine prostanooids from the Okinawan Soft Coral, Clavularia viridis. J. Nat. Prod. 1999, 62, 352–354. [CrossRef] [PubMed]

98. Corey, E.J.; D’Alarcao, M.; Matsuda, S.P.T.; Lansbury, P.T.; Yamada, Y. Intermediacy of 8-(R)-HPETE in the biosynthesis of marine prostanoids. J. Am. Chem. Soc. 1987, 109, 289–290. [CrossRef]

99. Corey, E.J.; Matsuda, S.P.T. Generality of marine prostanoid biosynthesis by the 2-oxidopentadienylcation pathway. Tetrahedron Lett. 1987, 28, 4247–4250. [CrossRef]

100. Watanabe, K.; Sekine, M.; Iguchi, K. Isolation and structures of new halogenated prostanooids from the Okinawan Soft Coral Clavularia viridis. J. Nat. Prod. 2003, 66, 1434–1440. [CrossRef] [PubMed]

101. Watanabe, K.; Sekine, M.; Iguchi, K. Isolation of three marine prostanooids, possible biosynthetic intermediates for clavulones, from the Okinawan Soft Coral Clavularia viridis. Chem. Pharm. Bull. 2003, 51, 909–913. [CrossRef]

102. Gerwick, W.H. Carbocyclic oxylipins of marine origin. Chem. Rev. 1993, 93, 1807–1823. [CrossRef]

103. Munro, M.H.G.; Luibrand, R.T.; Blunt, J.W. The search for antiviral and anticancer compounds from marine organisms. In Bioorganic Marine Chemistry; Scheuer, P.J., Ed.; Springer: Berlin/Heidelberg, Germany, 1987; pp. 93–176.

104. Baker, B.J.; Scheuer, P.J. The punaglandins: 10-chloroprostanooids from the octocoral Telessto riisei. J. Nat. Prod. 1994, 57, 1346–1353. [CrossRef]

105. Suzuki, M.; Morita, Y.; Yanagisawa, A.; Baker, B.J.; Scheuer, P.J.; Noyori, R. Prostaglandin synthesis 15. Synthesis and structural revision of (7E)- and (7Z)-punaglandin 4. J. Org. Chem. 1998, 53, 286–295. [CrossRef]

106. Armstrong, R.A.; Wilson, N.H. Aspects of the thromboxane receptor system. Gen. Pharmacol. 1995, 26, 463–472. [CrossRef]
107. Mustafa, T.; Srivastava, K.C. Prostaglandins (eicosanoids) and their role in ectothermic organisms. In Advances in Comparative and Environmental Physiology; Brouwer, M., Carr, W.E.S., Ellington, W.R., Engel, D.W., Gleeson, R.A., Korsgaard, B., Moerland, T.S., Mustafa, T., Prior, D.J., Sidell, B.D., et al., Eds.; Advances in Comparative and Environmental Physiology; Springer: Berlin/Heidelberg, Germany, 1989; pp. 157–207. ISBN 978-3-642-74510-2.

108. Kayama, M.; Sadō, T.; Iijima, N. The Prostaglandin synthesis in rainbow trout thrombocyte. NIPPON SUISAN GAKKAISHI 1986, 52, 925. [CrossRef]

109. Pettitt, T.R.; Barrow, S.E.; Rowley, A.F. Thromboxane, prostaglandin and leukotriene generation by rainbow trout blood. Fish Shellfish Immunol. 1991, 1, 71–73. [CrossRef]

110. Hill, D.J.; Hallett, M.B.; Rowley, A.F. Effect of prostanooids and their precursors on the aggregation of rainbow trout thrombocytes. Am. J. Physiol. 1999, 276, R659–R664. [CrossRef] [PubMed]