Review

Marine ecosystems may offer environmental drugs for interventions in immunoinflammatory rheumatic diseases

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ABSTRACT

Marine ecosystems boast a rich biodiversity and chemodiversity. In recent years, the bioprospecting and screening for bioactive compounds revealed the existence of a plethora of new potential therapeutics in the oceans. Among these are secondary metabolites with potential applications in human immunoinflammatory diseases to mitigate oxidative stress and pro-inflammatory responses. Molluscs, sponges, corals and other metazoans, but also photosynthetic microorganisms and seaweeds, produce bioactive compounds which interfere with the main pro-inflammatory pathways involved in the pathogenesis and progression of chronic inflammatory diseases and autoimmune disorders. Several marine compounds have already reached the pre-clinical and clinical stage of investigation, and some are expected to enter clinical practice soon. In this review we cover the recent advancements in marine drug discovery related to anti-inflammatory and immunomodulatory compounds and discuss their potential therapeutic applications.

Introduction

In clinical practice, the mainstay for the treatment of acute and chronic inflammatory diseases are synthetic drug formulations, such as aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (1). While these therapeutics are effective, their prolonged use can lead to harmful side effects, especially in patients suffering from chronic inflammatory diseases like rheumatoid arthritis (RA), the most common immune-mediated arthropathy (2, 3).

Natural anti-inflammatory compounds represent alternative solutions with fewer associated long-term risks and side effects (4). Marine environments have a long history as sources of bioactive compounds (5). The extremely rich marine biodiversity has gained increasing attention in recent years thanks to an intense bioprospecting activity and identification of novel therapeutic lead compounds. Not only microorganisms, but also metazoans, particularly invertebrates and their associated microbiota, and photosynthetic organisms like macroalgae, microalgae and cyanobacteria, produce a vast array of bioactive compounds with emerging pharmacological potential in the treatment of chronic inflammatory diseases and cancer (6-8). Among these, pigments and lipids represent the two main classes of compounds endowed with anti-inflammatory and immunomodulatory properties (Fig. 1) (9). Several marine-derived molecules have already entered the clinical trial stage, and many are currently being investigated in terms of mechanism of action in preclinical (10) studies (Supplementary Tables S1, S2, S3). Marine drug discovery activities are being conducted worldwide, with China being one of the leading countries, as reflected by a dedicated national Marine Materia Medica (11). Most marine compounds with market approval include anti-cancer drugs in the form of antibody-drug conjugates (12). Among the few examples of marine natural products being marketed as approved therapeutics is the oligosaccharide sodium oligomannate (marketed as GV-971, Shanghai Green Valley Pharmaceuticals, China) derived from a marine brown alga (13) and used in the treatment of Alzheimer's disease. The β-1,3/1,6-glucan (BG136) derived from the Kelp species (*Durvillaea antarctica*) is an oligosaccharide with es-

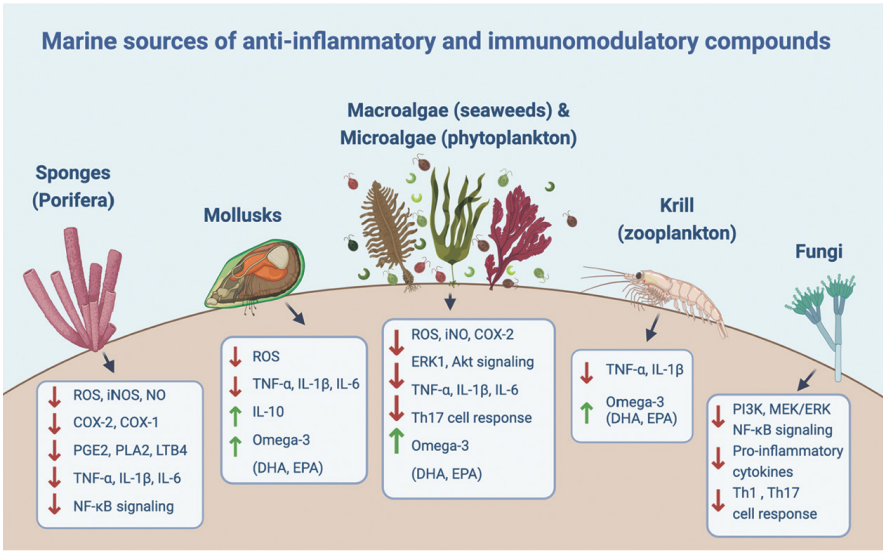

Fig. 1. Marine sources of anti-inflammatory and immunomodulatory compounds.
ROS: reactive oxygen species; iNOS: inducible nitric oxide synthase; NO: nitric oxide; COX-2: cyclooxygenase-2; COX-1: cyclooxygenase-1; PGE_2: prostaglandin E_2; PLA_2: phospholipase A_2; LTB_4: leukotriene B_4; TNF-α : tumour necrosis factor-α; IL-1β: interleukin-1β; IL-6: interleukin-6; IL-10: interleukin-10; NF-κB: nuclear factor kappa B; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; ERK1: extracellular signal-regulated kinase 1; Akt: protein kinase B; PI3K: phosphoinositide 3-kinase; MEK/ERK: mitogen-activated protein/extracellular signal-regulated kinase; Th1: T helper 1; Th17: T helper 17. The figure was created with www.biorender.com.

tablished applications in cancer immunotherapy being developed by Qingdao Marine Biomedical Research Institute, Ocean University of China, and CP Pharmaceutical (Qingdao) which entered clinical trial stage in 2022 (14-16).

In this review we offer a comprehensive summary of the state-of-the-art picture of marine-derived compounds highlighting their potential use as alternative and/or complementary therapeutic agents in the treatment of immuno-inflammatory diseases. We emphasize the relevance of marine biodiversity in the discovery of novel anti-inflammatory compounds.

Fish and krill oils

Fish oils are rich sources of omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). EPA and DHA are critical for the maintenance of the structure of cell membranes, influencing their fluidity and the function of membrane receptors (17). Moreover, marine oils interfere with the expression of several pro-inflammatory cytokines, including tumour necrosis factor (TNF)-α and interleukin (IL)-1β and alleviate pain and morning stiffness, thus reducing the need for NSAID consumption (18, 19). It is well established that higher serum levels of omega-3 (*e.g.*, EPA and DHA) fatty acids correlate with a lower activity of inflammatory processes compared with omega-6 (*e.g.* arachidonic acid) (20). For instance, it was reported that omega-3 fatty acids lower the risk of inflammatory arthritis in subjects presenting anti-citrullinated protein antibodies without a previous diagnosis of RA (21).

Moreover, a recent clinical study concluded that the intake of omega-3 fatty acids helped reduce RA inflammation and disease activity from disease onset, and omega-6 fatty acids were associated with lower disease activity after 6 months from onset (22). Overall, the dietary supplementation of marine (mainly fish) omega-3 fatty acids may support the standard pharmacological therapies in controlling disease activity and progression in various rheumatic diseases like RA, systemic lupus erythematosus (SLE) and osteoarthritis (OA) (23).

The Antarctic krill *Euphausia superba*, a small shrimp-like crustacean rich in EPA and DHA, is another valuable source of omega 3-fatty acids (24). Unlike traditional fish oils, where long-chain omega-3 fatty acids are predominantly found as part of triacylglycerols, krill oil contains these fatty acids mainly bound to phospholipids, which result in higher bioavailability (25-27). Notably, krill oil is rich in astaxanthin, a potent antioxidant carotenoid pigment (discussed later in more detail) (28,29). A recent randomised, double-blind trial involving patients with mild osteoarthritis of the knee or hip joint showed a significant pain-relieving effect and a good safety profile and safety of Krill Oil in combination with astaxanthin compared with lower molecular weight hyaluronic acid (30).

Another multicentre trial investigated the effects of a daily supplementation of krill-derived omega-3 rich oil in patients with SLE highlighting the beneficial impact on omega-3 deficiency which could be corrected within one month (31). Moreover, the disease activity was significantly reduced over the 24-week treatment period in the patient group displaying the highest activity at baseline (SLEDAI-2K ≥9). Therefore, fish oils, especially krill oil, are considered highly valuable food supplements of omega-3 fatty acids endowed with bioavailability, thus particularly effective in reducing joint pain and inflammation in OA, RA and SLE.

Marine invertebrates

Mollusca

A hallmark of the inflamed RA joint is a rapid decline in oxygen levels leading to increased production of reactive oxygen species (ROS). In turn, ROS activate the expression of pro-inflammatory genes like interleukin-1β (IL1β) and IL-6, resulting in extensive oxidative tissue damage (32). This environment also interferes with the activity of macrophages, promoting their switch towards the M1 pro-inflammatory phenotype (33). Antioxidant and anti-inflammatory compounds are therefore essential in mitigating oxidative and pro-inflammatory responses in RA patients. Extracts of *Paphia malabarica*, a marine bivalve native to south-eastern Asia, were recently shown to display anti-inflammatory activity *in vitro* using radical scavenging and anti-cyclooxygenase-2/5-lipoxygenase

assays (34). Other mussel-derived anti-inflammatory compounds were described recently (35). Among these, the green-lipped mussel (*Perna canaliculus*) native to New Zealand displays a high tissue content of omega-3 fatty acids, which have established antioxidant and anti-inflammatory properties (36-37). This bivalve is extensively used in traditional medicine and has been investigated in modern times to identify its bioactive components (38). In the 1990's, the extract of *Perna canaliculus*, known as Lyprinol was shown to exert inhibitory effects *in vitro* on the cyclooxygenase-2 and 5-lipoxygenase enzymes, thereby reducing the production of the proinflammatory mediator leukotriene B4 by human polymorphonuclear leukocytes, but also decreased prostaglandin E2 production by activated human macrophages (39).

Lyprinol effectively reduced the levels of inflammatory marker in a murine RA model without causing gastrointestinal toxicity or affecting platelet aggregation, a common side effect of prolonged NSAIDs use (40). More recently, lyprinol was tested in a clinical trial involving a cohort of 60 patients suffering from hip or knee osteoarthritis showing a significant reduction of pain and a progressive improvement of joint function (41). The beneficial effects of *Perna canaliculus*'s extracts have been highlighted in multiple clinical trials, in particular as an adjuvant treatment for osteoarthritis (42).

It was concluded that the high content of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is responsible for limiting the synthesis of inflammatory mediators, mainly prostaglandins and leukotrienes, by interfering with the arachidonic acid cascade, thereby reducing inflammation. The combined effect of lipids and flavonoids derived from *Perna canaliculus* and the blue mussel *Mytilus edulis* was also reported as an effective approach for the treatment of RA (43). The lipid extract from *Perna canaliculus*, containing over 60 bioactive compounds and known commercially as PCSO-524™ , is used to reduce physical discomfort and pain in patients diagnosed with osteoarthritis with comparable effects to traditional fish oil (44, 45). A randomised clinical trial enrolling 80 patients with moderate to severe hip or knee osteoarthritis treated with *Perna canaliculus* extract reported a significant reduction of joint stiffness and NSAIDs use in the post-intervention phase and a high safety profile (46). The same formulation was shown to alleviate pain after 2 months in a double-blind placebo-controlled clinical trial involving patients with knee osteoarthritis. Of note, the absence of gastrointestinal side effects highlighted the good safety profile of this dietary intervention (47, 48). The lipid extracts of the Korean mussel (*Mytilus coruscus*) have also been shown to inhibit the major pro-inflammatory signalling pathway Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) by reducing the synthesis of signalling pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), while promoting the release of the anti-inflammatory cytokine IL-10 in murine RA models (49). The emerging beneficial effects of Mollusca-derived lipids suggest their use as complementary dietary to alleviate inflammation thus and improving the overall quality of life.

Sponges (porifera)

Several marine sponges produce anti-inflammatory bioactive compounds which inhibit key pro-inflammatory mediators like TNF-α, IL-6, IL-1β, prostaglandin E2 (PGE2), nuclear transcription factor-kappa B (NF-κB), leukotriene B4 (LTB4), superoxide radicals and nitric oxide (NO) and the enzymes responsible for their production, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), phospholipase A2 (PLA2) and cyclooxygenase- 1 (COX-1) (50). For example, the sulfated sterol Solomonsterol A produced by the marine sponge *Theonella swinhoei* is a potent pregame-X-receptor agonist which was shown to attenuate systemic inflammation and immune dysfunction in a murine RA model (51). Similarly, the bioactive extracts from the sponge *Cliona celata* displayed a strong anti-inflammatory activity on lipopolysaccharide (LPS)- stimulated murine macrophages (52).

Marine fungi

Marine fungi produce a plethora of anti-inflammatory compounds. So far, around 150 molecules, predominantly produced by *Aspergillus* and *Penicillium* subspecies have been characterized in terms of mechanism of action (53). Several compounds interfere with key pro-inflammatory pathways and, in particular by disrupting the production of the mediators nitric oxide and prostaglandins, as demonstrated both *in vivo* and *in vitro* (53). One notable example is the phenolic compound 4-hydroxymethyl-catechol isolated from fungi of the *Pestalotiopsis* species, one of the several organisms composing the microbiota associated with marine sponges native to South Korea (54). 4-hydroxymethyl-catechol has been shown to modulate the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/NF-kB signalling pathway suppressing the pro-inflammatory response of helper T (Th)1 and Th17 CD4+ lymphocytes in human RA synovial fibroblasts both *in vivo* and *in vitro*. Along with the mitogen-activated protein kinase (MEK)/ extracellular signal-regulated kinase (ERK) pathway, PI3K and NF-κB play a pivotal role in the development and progression of the inflammatory response observed in RA, therefore their timely inhibition is crucial to mitigate the disease symptoms and to improve joint health (54, 55). This evidence suggests a feasible translation of -hydroxymethyl-catechol into clinical practice. Finally, the fungal symbiont *Aspergillus flocculosus* 16D-1 which lives in association with the sponge *Phakellia fusca*, showed an inhibitory activity against IL-6 production *in vitro*, suggesting its future use as a therapeutic agent (56). Furthermore, six new seco-terpenoids derived from marine fungus *Talaromyces aurantiacus* were shown to reduce NO production in LPS-induced inflammatory *in vitro* model (57).

Photosynthetic organisms: seaweeds and microalgae

Seaweeds

Seaweeds (or macroalgae) have been used in traditional medicine by coastal communities from immemorial time.

Several classes of seaweeds produce bioactive compounds, many endowed with anti-inflammatory and immunomodulatory properties. Brown algae (Phaeophyceae) contain the photosynthetic pigment fucoxanthin, which is a potent antioxidative agent known to stimulate the PI3K/Akt/Nrf-2 pathway *in vitro* (58). *Turbinaria ornata*, a brown alga native of the Pacific and Indian Oceans contains anti-inflammatory and antioxidant compounds displaying inhibitory effects *in vivo* against inflammation and bone damage, resulting in a marked reduction in the arthritic score and paw volume in murine models (59). The extracts from another edible brown macroalga, *Eisenia bicyclis*, were shown to suppress the expression of iNOS and COX-2 genes *in vitro* (60), while *Porphyra dentata's* extracts, a red edible seaweed, are rich in the phenolic compounds catechol and rutin, which suppressed NO production and the NF-κB pathway *in vitro* (61).
The extracts of the seagrass *Posidonia oceanica*, native Mediterranean Sea, modulate the ERK1/2 and Akt intracellular cascades, reducing the activity of iNOS and COX-2 (62). Similarly, a recent *in vitro* study highlighted the antioxidant activity of the crude polysaccharide extracts of the green seaweed *Halimeda tuna* (63). These initial evidences about bioactive compounds from macroalgae highlight the need to conduct more extensive bioprospecting studies to identify new sources of anti-inflammatory and immunomodulatory metabolites.

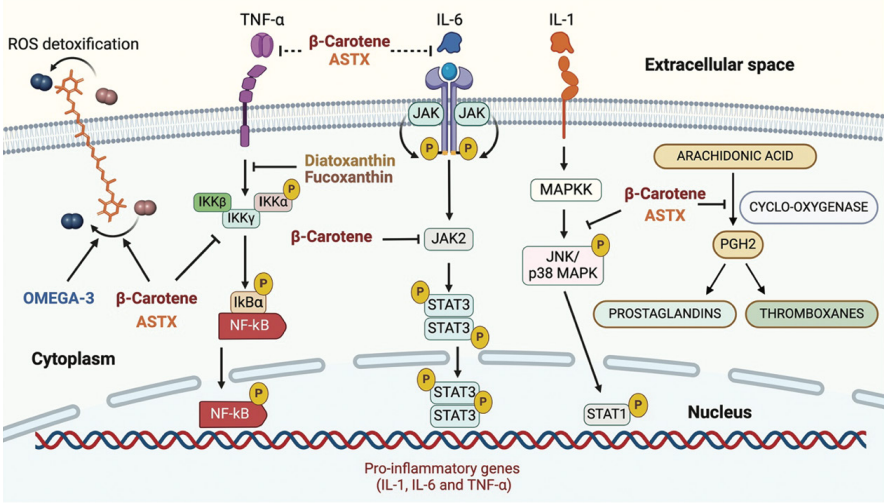

Fig. 2. Immunomodulatory and anti-inflammatory effects of marine bioactive compounds exerted at the intracellular level.
ROS: reactive oxygen species; TNF-α: tumour necrosis factor-α; IL-6: interleukin-6; IL-1: interleukin-1; IL-13: interleukin-13; ASTX: astaxanthin; IKKβ: IκB kinase β; IKKα: IκB Kinase α; IKKγ: IκB kinase γ; P: phosphorylation; IκBα: inhibitor of nuclear factor κB α; NF-κB: nuclear factor κB; JAK: Janus kinase; MAPKK: mitogen-activated protein kinase kinase; MAPK: mitogen-activated protein kinase; PGH_2: prostaglandin H_2; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; JNK: c-Jun N-terminal kinase; p38: p38 mitogen-activated protein kinase. The figure was created with www.biorender.com.

Microalgae

Microalgae comprise a vast group of photosynthetic prokaryotes and eukaryotes adapted to both freshwater and marine environments, including extreme habitats (Malavasi, Soru, & Cao, 2020; Varshney, Mikulic, Vonshak, Beardall, & Wangikar, 2015). Several microalgae are consumed in human nutrition as food supplements due to their high content of proteins and vitamins (64-73). Moreover, several species display a high cellular content of lipids, mainly polyunsaturated fatty acids (PUFAs), and photosynthetic pigments with established anti-inflammatory and immunomodulatory properties (74) (Fig. 2). Beside serving as natural sources of therapeutic compounds, microalgae are currently being tested for more advanced biomedical applications to produce biomaterials, drug delivery systems and for tissue engineering purposes (75-78). Moreover, microalgal lipids represent a more sustainable source of both omega-3 and omega-6 PUFAs compared with fish oils, but also a safer option, due to a lower risk of heavy metal contamination (79). Carotenoids are the most valuable class of secondary metabolites produced by microalgae. These lipid-soluble pigments consisting of a polyene chain are strong antioxidants which protect the photosynthetic apparatus from oxidative damage (Fig. 2) (80-81). Like all photosynthetic organisms, microalgae produce various carotenoid molecules. β-Carotene, an antioxidant molecule, is the precursor of retinol (vitamin A) in animals and is known to interfere with major pro-inflammatory pathways involved in the development and progression of RA and SLE (82-84). A strong correlation between the serum concentrations of antioxidant vitamins A and E and inflammatory markers in RA patients is well established (85) and the dietary intake of β-carotene, lycopene, vitamin C, and vitamin E is a major factor contributing to reduce the risk of developing hip osteoarthritis (86). Notably, lycopene extracted from the marine microalga *Chlorella marina* (Trebouxiophyceae) was reported to be more effective in reducing serum inflammatory biomarkers like erythrocyte sedimentation rate, white blood cell counts and C-reactive protein in a RA mouse model compared with that deriving from tomato (*Solanum lycopersicum*). Also, the microalgal compound was more effective in alleviating joint oedema (87). Lutein is found in several microalgal species, with the higher producers being the green microalgae (Chlorphyta) *Tetraselmis suecica* and *Tetraselmis chuii* (88, 89). Lutein is a strong antioxidant with potent anti-inflammatory properties (90) and the algal lutein from *Tetraselmis suecica* was shown to inhibit in a dose-dependent manner nitric oxide (NO) production and release of pro-inflammatory cytokines (TNF-α and IL-6) in murine models (88). Lutein from *Tetraselmis* species were also reported to inhibit *in vivo* the key inflammatory enzyme cyclooxygenase-2 (COX-2) and blocked the nuclear

factor-kB (NF-κB) pro-inflammatory pathway, causing the suppression of the release of inflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and TNF-α (91). Notably, cellular lutein content could be accrued via directed evolution in the GRAS/Novel food freshwater microalga *Chlamydomonas reinhardtii* (92), a species which serves as experimental model for translational research into industrially relevant strains.

Tetraselmis chuii is a non-toxic microalga which has been designated by the American Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) as generally recognised as safe (GRAS) and novel food, respectively (93, 94). The stress-resilient strain *Tetraselmis striata* is particularly attractive since it accumulates both anti-inflammatory pigments-like and lipids in response to environmental stresses, therefore it holds great promise as a natural source of bioactive compounds (95). The stress-resilient strain *Tetraselmis striata* is particularly attractive since it accumulates both anti-inflammatory pigments like lutein and lipids in response to environmental stresses, therefore it holds great promise as a natural source of bioactive compounds (95). Undoubtedly, the algal carotenoid of greatest therapeutical value is astaxanthin, which is known to promote bone homeostasis in degenerative skeletal diseases, including RA (96). Astaxanthin is the strongest antioxidant of natural origin, which is produced by few microalgal species (97-100), in particular the green microalga *Haematococcus lacustris* (previously *pluvialis*) (101, 102) a slow growing organism which accumulates the pigment only under stressing (excess light) conditions. Accordingly, a great focus is currently placed in the enhancement of astaxanthin production by its native producer by optimisation of culture conditions (103-109) and via metabolic engineering of fast-growing microalgae (110-114). Astaxanthin is known to interfere with the main pro-inflammatory pathways involved in the development and progression of chronic inflammatory disorders, including auto-immune diseases (115-124). It is therefore of great interest to develop efficient microalgae-based production platforms of this extremely valuable carotenoid, especially since the esterified biological astaxanthin displays higher bioavailability and is more effective compared with non-esterified synthetic versions (125, 126). Diatoms (127) and some haptophyte species like *Tisochrysis lutea* produce the carotenoid diatoxanthin, which is a strong antioxidant and has been shown to interfere in pro-inflammatory pathways associated with RA (128). The diatom *Phaeodactylum tricornutum* accumulates diatoxanthin and several bioactive PUFAs (omega 3-fatty acids) capable of inhibiting COX-2 enzymatic activity. Notably, diatom-derived EPA is approved for human consumption in the European Union (129-132). Moreover, the carotenoid fucoxanthin extracted from *Phaeodactylum tricornutum* was shown to mitigate IL-1β, IL-6, and TNF-α, secretion by inhibiting NF-κB and NLRP3-mediated inflammasome activation in cultured immune cells (133). *Pavlova lutheri* (Prymnesiophyceae) is another marine microalga belonging to the phylum Haptista with already established applications in cosmetics due to its rich content in omega-3 fatty acids (134, 135). Lipid extracts of *Pavlova lutheri* are enriched in EPA and DHA and were shown to exhibit anti-inflammatory effects by suppressing the production of the pro-inflammatory mediators IL-6 and TNF-α by activated human macrophages *in vitro* when provided in combination with extracts from the two red seaweeds *Palmaria palmata* and *Porphyra dioica* (136). The marine heterotrophic protist *Aurantiochytrium* (formerly *Schizochytrium*) holds GRAS/Novel Food status and is the highest DHA and EPA producer (137). Notably, the lipid extract of *Aurantiochytrium* (2.1 g DHA/day) displayed similar outcomes when compared with vegetable (sunflower) oil in a randomised clinical trial involving RA patients by reducing joint inflammation joints after a 10-week treatment (137).

The tremendous pharmacological potential of marine microalgae is expected to impact the most on the drug discovery research in the upcoming years and will be further enhanced by synthetic biology approaches to increase the accumulation of endogenous metabolites (138).

Mangrove habitats

Mangrove forests are unique tropical ecosystems created by salt-tolerant plants in which rich communities of microorganisms are found (139) These environments have recently emerged as sources of anti-inflammatory and immunomodulatory compounds of various origins. For instance, extracts of the mangrove *Aegiceras corniculatum* were shown to restrain the release of the pro-inflammatory cytokines TNF-α, IL-6, and IL-12 by cultured macrophages (140) while extracts of *Ceriops decandra* and *Excoecaria agallocha* suppressed the NF-κB pathway (141, 142).

Bridging biotechnology with environmental sustainability: the way forward

To ensure the continuous exploration of marine biodiversity for drug discovery, the exploitation of marine resources for medical purposes should be conducted in line with environmentally sustainable practices and consider the anthropogenic impact on biodiversity erosion. Marine ecosystems are already threatened by the various activities of the blue economy, namely intensive fishing, dredging and seabed mining, which pose a severe risk of species extinction (143-146). The ecological impact of seabed mining is already evident in microorganism biodiversity (147), the richest source of chemodiversity in the ocean. The consequences of anthropogenic climate changes are also already evident in invertebrate populations, such Antarctic krill, whose survival is threatened by rising water temperatures (148) but also on photosynthetic organisms like seaweeds, whose chemical composition is altered due to ocean acidification, a direct consequence of the rising of atmospheric CO_2 levels (149).

Biotechnology and bioengineering approaches offer an alternative solution

to the use of native producers to derive compounds of interest and, thus, might aid in the preservation of ecosystems. In this respect, microalgae are excellent platforms to produce heterologous compounds of interest. Their light-driven metabolism allows for low-cost large-scale cultivation and several species are amenable to genetic transformation. Beside boosting the accumulation of endogenous metabolites (pigments and lipids), genetic engineering can be harnessed in microalgae to achieve the synthesis of exotic metabolites and recombinant protein-based biopharmaceuticals (74).

Furthermore, emerging genetic engineering and synthetic biology tools are enabling the production of recombinant therapeutics in cyanoprokaryotes, including immunomodulatory proteins, opening new avenues for medical applications of photosynthetic microbes (150, 151).

Bringing marine compounds in the clinical practice

Marine-derived natural compounds have promising potential as adjuvant therapies for inflammatory diseases as shown in both *in vitro* and *in vivo* studies (Supplementary Table S1, S2, S3). Several natural compounds, like omega-3 fatty acids from marine invertebrates or antioxidant pigments from photosynthetic organisms could find immediate therapeutic applications to mitigate ROS production and to alleviate inflammatory symptoms. When integrated with conventional therapies, these marine-derived compounds may not only enhance anti-inflammatory effects but also reduce the dependency on prolonged NSAID use, which is frequently linked to severe gastrointestinal and renal side effects (2). Therefore, these novel bioactive compounds offer a complementary approach to improve overall treatment outcomes and patient quality of life. One challenge for the establishment of marine metabolites in routine clinical practice is the development of efficient drug delivery solutions, especially for poorly soluble compounds like photosynthetic pigments, to enhance their bioavailability (152-157).

More importantly, future randomised controlled trials in patients suffering from inflammatory diseases should investigate how these compounds should be integrated into clinical practice to achieve the optimal outcomes.

Conclusions

In summary, the ocean represents a vast resource for drug discovery and for deriving novel anti-inflammatory agents for clinical practice. The good safety profile of several compounds suggests their evaluation through larger and more comprehensive studies before entering regular use as complementary agents alongside, or even in substitution of, conventional therapies like NSAIDs. More research, however, is still required to assess their long-term effectiveness and synergistic effects with conventional therapies in patients with chronic inflammatory diseases. Moreover, a better understanding of the mechanisms of action is needed before introducing certain compounds, and combinations thereof, in the treatment of specific diseases and to better integrate them in clinical practice. A likely near future scenario will see marine bioactive compounds used as adjuvants to traditional medications, with the goal of reducing the dosages of conventional drugs and minimize their adverse effects. This integrative approach is expected to improve patient outcomes, but also to pave the way for more sustainable management of inflammatory conditions.

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