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AN UNTAPPED RESOURCE FOR NATURAL ANTI-INFLAMMATORY COMPOUNDS FROM MARINE MACROALGAE

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ABSTRACT

Marine algae are significant ingredients to formulate drugs for treating disease as they possess various bioactive potentials. This review expansively compares the anti-inflammatory compounds from different marine algae. The anti-inflammatory effects of several different crude extracts and pure compounds of algae have been evaluated.Natural products from marine algae have potential resources in discovering anti-inflammatory drugs. These bioactive compounds can be characterized and tested the efficacy of the future use for the public. Research institutions should collaborate with industry in order to design and develop suitably appealing products with these bioactive compounds.

KEYWORDS: **Bioactive, Seaweeds, Eicosanoids, Drugs**

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INTRODUCTION

In the planet, 70% covers marine environment which have diverse life forms that constitute a rich resource for the development of a wide range of applications[1,2]. Seaweeds or marine algae provides prolific sources of highly bioactive secondary metabolites that might represent useful leads in the development of new pharmaceutical agents[3].India has a long coastline extending to 8085 kms and the seaweed industry depends entirely on the natural stock of seaweeds. Seaweeds possess wide application in food and pharmaceutical industries, however, the seaweed of the Indian coastal area are still unexplored. The objective of this review is to highlight some of the recent developments and findings in the pharmacological application of seaweeds with special reference to the anti-inflammatory potential of marine macroalgae.

INFLAMMATION

Inflammation is part of the body's immune response when something harmful or irritating affect. A main role of inflammation is to resolve the infection, elimination of invading pathogens and toxins and to repair the damage in order to achieve homeostasis equilibrium[4]. An over activation of innate immune response can cause chronic infection or chronic inflammation due to an inefficient regulation or resolution of the inflammatory response[5]. It is typified by redness, swelling, heat, pain and loss of function and involves interactions amongst many cell types and the production of, and responses to, a number of chemical mediators[6]. The inflammatory response involves the sequential activation of various signaling pathways, including prostaglandins (PGs), cyclooxygenases (COX), nitric oxide synthase (NOS), cytokines, and many more[7].

INFLAMMATORY MEDIATORS

The controlled inflammatory responses are essential to remain healthy. Though, disproportionate inflammation leads to a variety of acute and chronic human diseases. They are characterized by the production of inflammatory cytokines, arachidonic acid– derived eicosanoids (PGs, thromboxanes (TXs), leukotrienes (LT), and oxidized derivatives), other inflammatory agents and adhesion molecules. Inflammation has been linked to the pathogenesis of many diseases like cancer, atherosclerosis, neurodegenerative diseases, diabetes mellitus, obesity, arthritis, cardiovascular diseases, Parkinson's disease and other deadly diseases[8-11]. Hence, inhibition of the high level of inflammatory mediators should be a useful approach to treat disease conditions.

ANTI-INFLAMMATORY

Any substances that inhibit production of inflammatory molecules are considered as potential anti-inflammatory agents[12]. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids which affect the central nervous system. Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to relieve pain and reduce signs of inflammation: fever, swelling and redness. However, various side effects of long term use of these drugs have been described. In addition, anti-inflammatory drugs are used mainly to alleviate the symptoms of the disease without actually treating or preventing the inflammatory processes. These pharmaceutical problems point that we are now at the crucial stage where it is essential to develop novel drugs and to explore new strategies in order to combat inflammatory diseases.

MARINE MACROALGAE

An increasing number of studies on widely distributed marine flora and fauna are demonstrating that many compounds produced by marine life have useful pharmacological activities. Among these organisms, the macroalgae is considered to be a rich sources of structurally diverse bioactive substances with great pharmaceutical potential[13-15]. Seaweeds are classified as Rhodophyta (red algae), Phaeophyta (brown algae) or Chlorophyta (green algae) depending on their nutrient, pigments and

chemical composition. They have been considered safe, less toxic, readily available and even through their modes of action are yet infinite for the most part[16].

INDIAN SCENARIO

Approximately 841 species of marine algae found in both inter-tidal and deep water regions of the Indian coast[17]. They are abundantly found in Gujarat, Madhya Pradesh, Andhra, Southern Tamil Nadu coast. Seaweed harvest across the Indian coast is about 100,000 metric tons (wet weight)[18]. Although, seaweeds in India are used for industrial production of agar, alginate and as a fertilizer, it is yet to be utilized on a large scale for various purposes, which is not being done, due to lack of its awareness among the Indian populace[18].

FOOD AND MEDICINAL COMPOUNDS

Marine macroalgae are the sustainable resources which have been used as a source of food and medicine. It was estimated that about 90% of the species of marine plant are algae, and about 50% of the global photosynthesis is contributed from algae. Seaweeds are widely used as food, as ingredients in cosmetics and fertilizers, and in hydrocolloid production such as agar and alginate[19]. Half of the primary production is depended on seaweeds for the worldwide food chain[20]. Seaweeds cannot be considered as a main source of energy, but they have nutritional value regarding vitamin, protein and mineral contents[21]. Ancient people believed that seaweeds have the ability to cure diseases and prolong life[22]. Around ninety percent of the global seaweed industry is used directly for human consumption.Marine algae has developed different defense strategies to survive in a competitive environment, that result in a significant level of structural– chemical diversity, from different metabolic pathways[23,24]. Seaweeds produce a variety of compounds such as carotenoids, terpenoids, xanthophylls, chlorophyll, vitamins, saturated and polyunsaturated fatty acids, amino acids, acetogenins, antioxidants such as polyphenols, alkaloids, halogenated compounds and polysaccharides such as agar, carrageenan, proteoglycans, alginate, laminaran, rhamnan sulfate, galactosyl glycerol and fucoidan[25-34]. Many of these compounds are known to possess biological activity and hence have potential advantageous use in healthcare. Seaweeds found growing in abundance off the coastal areas of many parts of the world represent a huge yet untapped potential for new source of therapeutics[18,35]. Seaweed is exposed to light and high oxygen concentrations that induces the formation of inflammatory mediators, including nitric oxide (NO) and reactive oxygen species (ROS)[36]. Recently, various types of marine algae, including inedible seaweed are reported to protect against gastrointestinal injury, peptic ulcers and liver injury, as well as possessing anti-inflammatory, antioxidant and anticoagulant activities[37-39]. Seaweeds have enormous potential as components of fertilizers, in animal feed supplements, and as additives in human food. The nutritional value of macroalgae makes them particularly appropriate for use in the food industry. Seaweeds that have played significant roles in drug discovery and development, especially anti-inflammatory agents against several diseases[40].

SECONDARY METABOLITES-APPLICATION IN HUMAN HEALTH

Secondary metabolites are organic compounds synthesized from algae to protect themselves and to maintain homeostasis in their environment. The protein content of brown seaweeds is generally small (average: 5 - 15% of the dry weight), whereas higher protein contents are recorded in green and red seaweeds (on average 10 - 30% of the dry weight) [41].

POLYSACCHARIDES

Different polysaccharides are present in seaweeds, which are chemically related to the corresponding taxonomic classification of algae and their cell structure[42,43]. The total dietary fiber content is higher than the fiber content of most fruits and vegetables, that seaweeds ranges from 29.3–62.3g/100g[44-46]. Polysaccharides have anti-inflammatory, antiviral, anti-tumor and antioxidative activities[47,48]. One can refer O'Sullivan et al[49] for the detailed chemistry and structure of the polysaccharide present in seaweeds. Alginates are absent in terrestrial

plants and present in seaweeds, found to have strong antibacterial and anti-inflammatory activities[50]. Fucoidans is a fucose-enriched sulfated polysaccharides found in the extracellular matrix of brown algae. Heo et al[36] explained the anti-inflammatory activity of fucoxanthin by suppressing NO production and iNOS expression, which may be associated with the attenuation of tumor necrosis factors α (TNF-α) formation in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. Porphyran, makes up the main components of the red macroalga. It is reported as a gelling agent, a nutritional supplement and as an antioxidant[49,51].

POLYUNSATURATED FATTY ACIDS (PUFAS)

Seaweeds are a well known source of polyunsaturated fatty acids (PUFAs), primarily as components of complex lipids[52]. PUFAs regulates a wide-ranging of functions in the body including blood pressure, blood clotting, functioning of the brain and nervous systems[53]. Two essential classes of PUFAs, the n-6 (ω6) and n-3 (ω3) classes are essential because we cannot make them in our bodies. Some marine algae, which can be used as foods are reported to contain high levels of ω -3 PUFAs. ω3 polyunsaturated fatty acids have confirmed to have anti-inflammatory activity *in vivo* and *in vitro*[54,55]. Many algae that can convert simple polyunsaturated fatty acids such as arachidonic acids (AA; 20; 4n-6) into complex eicosanoids and related oxylipins has been an exciting development[56]. The term 'oxylipin' is used to encompass the C-20 eicosanoids as well as partially-oxidized fatty acids of shorter chain length[57]. In humans, these PUFAs are metabolized by a variety of oxidative enzymes to the PGs, TXs, LT, hydroxyeicosatetraenoic acids (HETE) and are collectively known as eicosanoids[58]. C_{18} and C_{20} oxylipins derived from AA metabolism in marine macroalgae possess novel chemical structures not found in mammalian AA metabolism, leading to a wide variety of bioactive natural products[58]. Normal metabolism of PUFAs in seaweeds can lead to the production of eicosanoids which involved in the regulation of immunity, inflammation, and neurotransmission[59]. AA and eicosapentaenoic acid (EPA) hydrolyzes from phospholipids by phospholipases A2[60]. AA metabolism through COX, lipoxygenase (LOX) and cytochrome P-450 epoxygenase (EPOX) pathways leads to the generation of biologically active eicosanoids, including PGs, LTs, HETEs, epoxyeicosatrienoic acid (EETs) and hydroperoxyeicosatetraenoic acids (HPETE)[61]. Bi-functional enzyme COX (COX-1 and COX-2) that converts AA to prostaglandin G2 (PGG2) and another site that reduces PGG2 to prostaglandin H2 (PGH2)[62,63]. The COX isoforms, COX-1 and COX-2 are similar in size, substrate specificity and kinetics, however, differ in their expression and distribution . Dietary supplementation with n-3 PUFAs causes a reduction in the expression and activity of aggrecanases, inflammation-inducible cytokines, and cyclooxygenase-2, but not the constitutively expressed COX-1[64].The 2-series PGs are generally thought as being pro-inflammatory[65], anti-inflammatory properties have also been ascribed to them by suppressing proinflammatory cytokine and lymphokine production[66]. PGE_2 inhibits 5-LOX and promoting the formation of lipoxins by inducing 15-LOX[67,68]. Vascular cells are the major source of PGI_2 that regulates cardiovascular homeostasis[69]. PGI_2 is rapidly produced following tissue injury or inflammation and it is the most abundant prostanoid in synovial fluid in human arthritic knee joints[70,71].PGD_2 is a major eicosanoid that is synthesized in both the central nervous system and peripheral tissues. It involved in the regulation of sleep and other central nervous system activities, including pain perception[72,73]. PGD_2 can be further metabolized to $PGF_{2\alpha}$, 9α,11β-PGF_2 and the J series of cyclopentanone PGs, including PGJ2, Δ^{12}-PGJ_2, and 15d-PGJ_2. COX-2 products PGD_2 and 15d-PGJ_2 are involved in the resolution of inflammation[74].4-series LTs metabolized by LOX from the omega-6 family of eicosanoids. The production of LTs, HETEs and leukotriene B4 (LTB4) comprise a group of mediators derived from the action of LOX on AA. EPA was also reported as being a substrate for AA cascade enzyme pathways, in which it induced the production of other eicosanoids such as 3-series prostanoids and 5-series leukotrienes[75]. EPA/docosahexaenoic (DHA) replace linoleic acid and AA, the main substrates to produce eicosanoids by COX, LOX,

and EPOX pathways[76]. Fish is the main source of EPA (C20:5n-3) and of DHA (C22:6n-3)[77].E-series resolvins formed from EPA by a series of reactions involving COX- 2 (acting in the presence of aspirin) and 5-LOX. DHA-derived trihydroxydocosahexanoic acid mediators termed D-series resolvins. These mediators appear to exert potent anti-inflammatory actions in neutrophils, macrophages, dendritic cells and T cells[78-81]. Ethanolic extract of *Codium fragile* showed the inhibition of NO and PGE_2 production in LPS-stimulated RAW 264.7 cells is mediated through the nuclear factor (NF-κB)-dependent transcriptional down regulation of iNOS and COX-2[82]. The green alga *Ulva lactuca* was shown to possess an anti-inflammatory compound[83].

NUCLEAR FACTOR (NF-KB)-PATHWAY

Nuclear factor (NF-κB) plays a crucial role in the early stages of immune and acute phase inflammatory responses, as well as in cell survival[84]. The activation of NF-κB by proinflammatory cytokines such as interleukin 1 (IL-1), TNFα, and the expression of other proinflammatory genes, including cytokines, chemokines, and adhesion molecules and enzymes such as inducible nitric oxide synthase (iNOS) and COX-2[84-86]. NF-κB contributes to the feedback control of inflammation by various mechanisms to affect the magnitude and duration of the inflammatory response[86]. NF-κB activation is also widely implicated in inflammatory diseases[87] and has focused on the development of anti-inflammatory drugs targeting NF-κB[88].

EXTRACTION OF EICOSANOIDS FROM MACROALGAE

The active principles should extract without loss of their activity. It is important to consider the extraction procedure that should be selective, cost-effective, and environmentally friendly extraction procedures. One of the more surprising groups of natural products to find wide distribution in the marine environment are the eicosanoids and related fatty acids[56]. List of seaweed species, eicosanoid molecules, organic solvents used for extraction and anti-inflammatory model used in assays are shown in Table 1. Different seaweeds collected from Mandapam, Tamil Nadu, East coast of India shown in Fig 1.

RED ALGAE

First report of PGs in plants was the isolation of PGE2 and PGF2 from the Australian red alga, *Gracilaria lichenoides*[89]. Sajiki and Kakimi[90] identified PGE, 15-keto-PGE, 8- HETE, PGA , LTB from *Gracilaria asiatica* with the help of high performance liquid chromatography- mass spectrometry (HPLC –MS). This species of red algae contain a high percentage of AA. PGA_2 reported from *Gracilaria verrucosa* that appears to be responsible for a gastrointestinal disorder, known as “ogonori” poisoning in Japan[91]. With the help of Ultraviolet (UV) and HPLC, Burgess *et al*. (1991) identified 5(Z),8(Z),10(E},12(E),14{Z)-eicosapentaenoic acid molecule in *Bossiella orbigniana*. Hsu et al[92] has developed HPLC methodology to identify PGE_2 from *Gracilaria gigas*.The fatty acid constituents of the red alga *Gracilariopsis lemaneiformis* have been investigated and their chemical structures determined by various spectroscopic methods. The identified compounds are 12S-HETE; 12S-HEPE, 12R, 13S-diHETE;12R, 13S-diHEPE. The occurrence of these different eicosanoids in *G. lemaneiformis* suggests that this red algae may contain several oxidative enzymes[93].*Rhodymenia pertusa* contains 6-trans-leukotrieB_4, 5R,6S-diHETE; 5R,6S-diHEPE[56]. The occurrence of 5R,6S-diHETE, 5R*,6S*-diHEPE, 5-HETE, 5-HEPE metabolites strongly suggests that *R. pertusa* contains a unique 5R-lipoxygenase system acting on both arachidonic and eicosapentaenoic acids[94]. Moghaddam et al[95] reported the first isolation of LOX product, hepoxilin B3, from the tropical red marine algae *Platysiphonia miniata* and *Cottoniella filamentosa*. The structural description of these algal natural products was identified by two-dimensional nuclear magnetic resonance (NMR). The croton oil-induced mouse ear edema test is widely used together with the in vitro phospholipase A2 (PLA2) assay to screen the anti-inflammatory compounds[96,97]. Marine red alga *Galerina marginata* displayed anti-inflammatory activity in its apolar extract.

Thus, as PLA2 controls inflammatory responses, the edema reduction in the mouse ear indicated that the apolar extract from *G. marginata* influences PLA2 activity[98]. Methanol extracts of *Gracilaria edulis* were subjected to paw edema, anti-inflammatory test. The seaweed extract had equally good anti-inflammatory effects in the carageenan induced paw edema compared to those of the standard drugs (Diclofenac) ($P<0.05$)[99].Vázquez et al[15] were investigated the anti-inflammatory and analgesic effects of red seaweed *Dichotomaria obtusata*, using classic tests in mice (ear edema induced by TPA and writhing induced by acetic acid). The results showed that *D. obtusata* inhibited mouse ear edema and significantly reduced abdominal writhes. Phenolic compounds (catechol, rutin and hesperidin) were identified in the methonolic crude extract of *Porphyra dentata*[100]. The crude extract and the phenolic compounds inhibited the production of NO in LPS-stimulated RAW 264.7 cells. Catechol was a more potent suppressor of the up-regulation of iNOS promoter and NF-$_k$B enhancer than rutin and yet, hesperidin alone failed to inhibit either activity.Ethyl acetate extracts from three seaweeds, *Laurencia okamurae*, *Grateloupia elliptica* and *Gloiopeltis furcata* were potent inhibitors of the production of pro-inflammatory mediators such as NO, PGE_2, IL-6 and TNF-α[101]. The anti-inflammatory activity of the isolated compounds from *Gracilaria verrucosa* was evaluated by determining their inhibitory effects on the production of pro-inflammatory mediators (NO, IL-6, and TNF-α) in LPS-activated RAW 264.7 murine macrophage cells[102].Total inhibition of PLA2 was observed in the extracts of *Asparagopsis armata, Chondrus crispus and Gelidium sesquipedale*. Also, extract of *Corallina elongata, Chondria dasyphylla*, *Laurencia pinnatifida, Gigartina acicularis, Pterosiphonia complanata* and *Palmaria palmata* showed anti phospholipase activity with an inhibition percentage higher to 70%. Red algae is said to be rich in sulfated polysaccharides, fucanoids and ω-3 fatty acids which are commonly associated with anti inflammatory activity. The ω-3 PUFAs is mainly known for their anti-inflammatory effects, which are related to their competition as substrates for COX and LOX that leads to decreased production of PGs and LTs[103].

BROWN ALGAE

Aqueous extract of *Turbinaria conoides* was evaluated for its anti-inflammatory effect using ethyl phenylpropiolate (EPP) -induced ear edema and carrageenin-induced hind paw edema tests. Results revealed anti-inflammatory activity of *T. Condos* comparable to that phenylebutazol and acetylsalicylic acid used as standard controls[104].Methyl ester derivatives [methyl 12-[1'(Z), 3'(Z) -hexadienyloxy] -6 (Z), 9 (Z), 11 (E) -dodecatrienoate, methyl 12-[1'(Z), 3'(Z) -hexadienyloxy] -9 (Z), 11 (E) -dodecadienoate, methyl 14-[1'(Z), 3'(Z) -hexadienyloxy] - 5 (Z), 8 (Z), 11 (Z), 13 (E) -tetradecatetraenoate, and 13 (S) -hydroxy-6 (Z), 9 (Z), 11 (E), 15 (Z) -octadecatetraenoic acid] were identified from *Laminaria sinclairii* (Proteau and Gerwick, 1993). 13 (S) -hydroxy-6 (Z), 9 (Z), 11 (E), 15 (Z) -octadecatetraenoic acid have been isolated from *L. Sinclair*, *L. saccharina* and *L. setchellii* as their methyl ester derivatives[105]. The presence of these compounds in brown algae strongly suggests that these organisms possess an active LOX with ω-6 specificity.Qualitative analysis of chloroform/methanol extracts of the cell culture biomass by Gas chromatography–mass spectrometry (GC-MS) confirmed the presence of the hydroxy fatty acids 13-HODTA and 13-HOTE, the likely products of 15-LOX catalyzed oxidation of linoleic or linolenic acids from *Laminaria saccharina*[57].ATD-2 (stearidonic acid: SA), ATD-4 (EPA) and ATD-9 (AA) were isolated from the edible brown seaweed *Undaria pinnatifida*. SA was active against mouse ear inflammation induced by phorbol myristate acetate, with IC50 values of 160, 314, and 235g per ear for edema, erythema, and blood flow, respectively. EPA was also active against edema, erythema, and blood flow, with IC50 values of 230, 462, and 236 g per ear, respectively. Although AA at low concentrations showed anti-inflammatory activities[106]. *U. pinnatifida* has been used to treat urinary diseases and dropsy in China[107]. The seaweed is also known to contain SA, which inhibits leukotriene production in inflammation[108]. Most of

these effects are directly or indirectly related to the anti-inflammatory action of the seaweed. Hong et al[109] reported that, 500 mg/kg body weight of methanolic extract of *Sargassum swartzii* induced analgesic protective effect against both thermal stimuli and the writhing syndrome indicating central and peripheral effects. This result shows *S. swartzii* possess a dose-dependent anti-inflammatory effect against both acute (exudative) and chronic (proliferate) inflammation. *Petalonia binghamiae* potently inhibited LPS-induced NO and PGE2 production, exhibiting IC50 values of 38.8 and 9.3 µg/mL. Consistent with these findings, *P. binghamiae* reduced the LPS-induced expressions of iNOS and COX-2 at the protein level in a concentration-dependent manner, in addition, the levels of TNF-α and IL-6 released into the medium were reduced by *P. binghamiae*, exhibiting IC50 values of 19.4 µg/mL for IL-6[101]. Yoon et al[82] found that *Sargassum micracanthum* significantly inhibited the production of the pro-inflammatory cytokines and their mRNA expression. NF-kB plays a critical role in the regulation of cell survival genes and coordinates the expressions of pro-inflammatory enzymes and cytokines such as iNOS, COX-2, TNF- IL-1ß, and IL-6. Since the expressions of these pro-inflammatory mediators are modulated by NF-kB. Yoon et al[82] findings suggest that the transcriptional inhibition of pro-inflammatory mediator production by *S. micracanthum* occurs via blocking of the NF-kB signaling pathway.The dichloromethane extract (0.4 mg/ear) of *Sargassum fulvellum* inhibited an inflammatory symptom of mouse ear edema by 79.1% and ethanol extract (0.4 mg/ear) of *Sargassum thunbergii* inhibited edema by 72.1%[101,110]. These findings are consistent with various claims that these seaweeds can be used as remedies for inflammation-related symptoms[110].The data obtained by Cumashi et al[111] demonstrate that fucoidans from brown algal species different from the traditionally studied *Fucus vesiculosus* and *Ascophyllum nodosum* may act as inhibitors of inflammation, angiogenesis, and heterotypic tumor cell adhesion. Pretreatment with the ethonolic and hexane fraction of *Myagropsis myagroides* decreased mRNA and protein levels of inducible NO synthase and COX-2, resulting in a decrease in NO and PGE2 in LPS-stimulated BV-2 cells. Furthermore, both extraction inhibited the production of inducible pro-inflammatory cytokines at their transcriptional level via inactivation of NF-κB[112,113]. One of the anti-inflammatory compounds in ethanolic extraction was identified as 6,6'-bieckol[112].

GREEN ALGAE

Green algae has less potential on anti-inflammatory compounds as compared with red and brown algae. Pheophytin a chlorophyll-related compound from *Enteromorpha prolifera* has a potent anti-inflammatory activity. The suppressive effects against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced superoxide anion generation in mouse macrophages, N-formyl-methionyl-leucyl-phenylalanine (FMLP)-induced chemotaxis of human polymorphonuclear cells (PMNs) and TPA induced edema formation in mouse ears[114].*Ulva lactuca* the green alga available in Tuticorin coast was found to show anti-inflammatory effect as evidenced by the reduction in the inhibition of edema on the 4th day of the experiment compared with the positive control drug and control[115]. Methanol extracts of *Ulva conglobata* and *U. lactuca* have shown anti-inflammatory effects in experiments that used a murine hippocampal HT22 cell line[116]. The other highly active species, *Ulva linza* (L.) J. agardh, is well-known as one of the bloom forming green seaweeds in the eutrophic area. This species showed microalgal growth enhancement[117], antiviral activity[118] and an allelopathic effect on the red tide *Prorocentrum micans*[119]. Purified component lycopene from *Chlorella marina*, which confirmed the anti-inflammatory effects in a rat model of arthritis[120].

Table 1
Anti-inflammatory compounds from different seaweeds

S.No	Seaweed	Compounds	Extraction/Analysis	Antiinflammatory Activity model	Reference
Red algae					
1.	*Gracilaria asiatica*	Prostaglandin (PG) E , 15-keto-PGE , 8-hydroxyeicosatetraenoic acid (HETE), PGA , leukotriene B	HPLC and MS		90
2.	*Galaxaura marginata*		Polar extract/TLC	Croton oil in mouse ear	98
3.	*Gracilariopsis lemaneiformis*	12S-HETE; 12S-HEPE, 12R, 13S-diHETE;12R, 13S-diHEPE			93
4.	*Gracilaria lichenoides*	Prostaglandins PGE_2, PGF2α			89
5.	*Gracilaria verrucosa*	PGE_2			91
		PGA_2			121
6.	*Rhodymenia pertusa*	6-trans-leukotrieB_4, 5R,6S-diHETE; 5R,6S-diHEPE			56
7.	*Rhodymenia pertusa*	5R,6S-diHETE, 5R*,6S*-diHEPE, 5-HETE, 5-HEPE	NMR and MS		94
8.	*Cottoniella filamentosa*	Hepoxlin B_3			95
9.	*Polyneura latissima*	9-HETE			56
10.	*Gracilaria edulis*			Paw edema	99
11.	*Dichotomaria obtusata*		Water	Ear edema induced by TPA and writhing induced by acetic acid	15
12.	*Phorphyra dentate*		Methanol/ HPLC, ESI-MS and UV	LPS induced RAW 264.7 macrophages	100
13.	*Galaxaura marginata*		Ethanol:acetic/TLC	Croton oil induced mouse ear edema	98
14.	*Laurencia okamurae, Grateloupia elliptica, Gloiopeltis furcata,*		Ethyl acetate	Mouse macrophage cell line RAW 264.7	40
15.	*Gracilaria gigas*	PGF_2, PGE_2, PGA_2	HPLC		92
16.	*Bossiella orbigniana*	5(Z),8(Z),10(E},12(E),14{Z)-eicosapentaenoic acid.	UV, HPLC		122
17.	*Gracilaria Verrucosa*		Methanol/RP-HPLC, NMR and MS	lipopolysaccharide (LPS)-activated RAW 264.7 murine macrophage cells	102
18.	*Gracilaria verrucosa*	Polysaccharide water soluable Fraction		Mouse - Immunostimulant activity	123
Brown algae					
19.	*Turbinaria conoides*		Water or ethanol	EPP-induced ear edema; Carrageenin-induced hind paw edema.	104

20.	*Laminaria setchellii, L. sinclairii, L. saccharina*	15S-HETE, 15S-HEPE, 13S-HOTE1, 3S-HODTA			105
21.	*Laminaria saccharina*	13-HODTA, 13-HOTE	Chloroform-methanol extracts/ GC-MS		57
22.	*Undaria pinnatifida*	ATD-2 (stearidonic acid: SA), ATD-4 (eicosapentanoic acid: EPA) and ATD-9 (arachidonic acid: AA)	RP-HPLC, GC-MS, NMR	PMA-induced mouse ear inflammation symptoms of edema, erythema, and blood flow.	106
23.	*Padina tertastomatica* and *Sargassum wightii*			Paw edema	99
24.	*Sargassum swartzii*		Methanol	Carrageenan-induced hind paw edema in rats and Peritonitis for acute and chronic inflammatory models	109
25.	*Petalonia binghamiae*		Ethyl acetate	LPS induced RAW 264.7 macrophages	101
26.	*Sargassum micracanthum*		Ethanol/ Hexane and CH_2Cl_2 fractions	LPS induced RAW 264.7 macrophage	82
27.	*Sargassum thunbergii and Sargassum fulvellum*		Ethanol, boiling water and Dichloromethane	Taphorbol myriste acetate-induced ear edema, erythema, and blood flow	110
28.	*Sargassum thunbergii, Hizikia fusiformis*		Ethyl acetate	Mouse macrophage cell line RAW 264.7	40
29.	*Ecklonia cava*	Polysaccharide	Anion-exchange chromatography, Gel filtration chromatography	Murine macrophage cell line RAW 264.7	124
30.	*Fucus vesiculosus, Ascophyllum nodosum*	Fucoidans	Gel-permeation chromatography	Rat peritoneal inflammation model	111
31.	*Myagropsis myagroides*		Ethanol-Hexane fraction/Western blot	Lipopolysaccharide-stimulated BV-2 microglial cells	113
32.	*Myagropsis myagroides*	Fucoxanthin	Methanol/Column chromatography, HPLC	Murine macrophages and mouse ear edema	112
Green algae					
33.	*Caulerpa racemosa*			Paw edema	99
34.	*Ulva reticulata*		Methanol	Carrageenan-induced hind paw edema in rats and Peritonitis for acute and chronic inflammatory models	109
35.	*Enteromorpha prolifera*	Pheophytin	TLC, HPLC	Edema Formation test in mouse ear	114

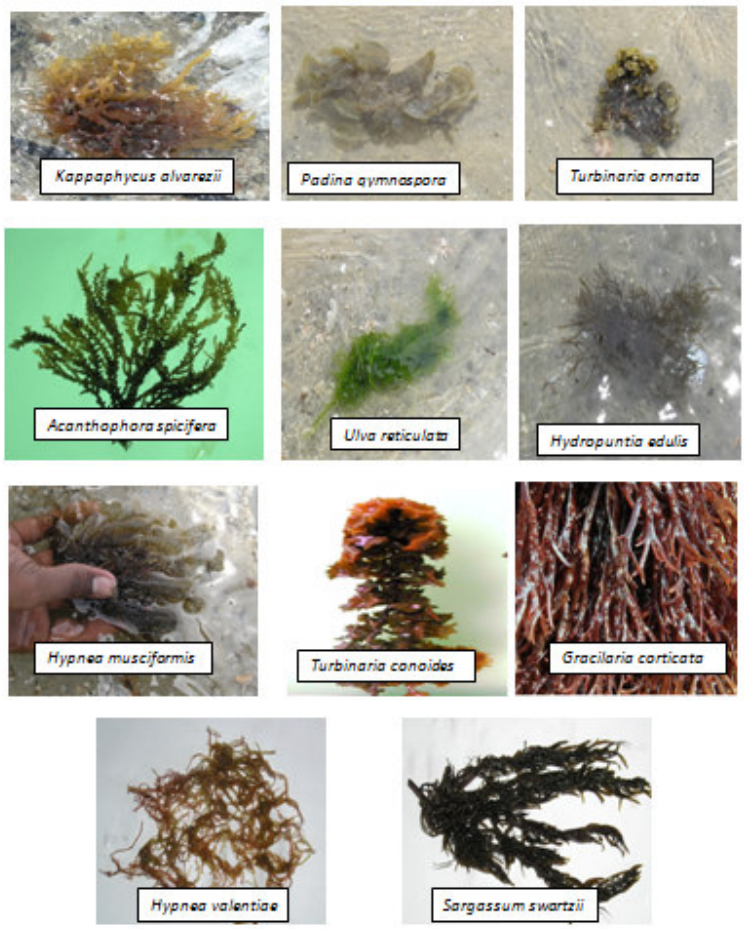

Figure 1
Different seaweeds collected from Mandpam, Tamil Nadu, South east coast of India

CONCLUSION

There was a remarkable increase in marine anti-inflammatory pharmacology research in past ten years. The molecular mechanism of action of several marine natural products, which were shown in preclinical pharmacological studies to target neutrophils and macrophages both *in vitro* and *in vivo*, was reported in several publications. Marine algal natural products are rich sources of antioxidants. In the future, these marine algae-derived compounds will be used more often in pre-clinical studies for drug discovery.

LIST OF ABBREVIATIONS

PGs-Prostaglandins; COX-Cyclooxygenases; NOS-Nitric oxide synthase; NSAIDs- Nonsteroidal anti-inflammatory drugs; NO-Nitric oxide; ROS-Reactive oxygen species; PUFAs-Polyunsaturated fatty acids; TNF-α-Tumor necrosis factors α; AA-Arachidonic acids; TXs-Thromboxanes; LT-Leukotrienes; HETE-Hydroxyeicosatetraenoic acids; EPA-Eicosapentaenoic acid; LOX-Lipoxygenase; EPOX-Cytochrome P-450 epoxygenase; EETs-Epoxyeicosatrienoic acid; HPETE-Hydroperoxyeicosatetraenoic acids;LTB4-Leukotriene B4; DHA-Docosahexaenoic; NF-kB-Nuclear factor; IL-1-Interleukin 1; iNOS-Inducible nitric oxide synthase; HPLC-MS-High performance liquid chromatography- mass spectrometry; UV-Ultraviolet; NMR-Nuclear magnetic resonance; PLA2-Phospholipase A2; GC-MS-Gas chromatography–mass spectrometry; SA-Stearidonic acid; TPA-2-O-tetradecanoylphorbol-13-acetate;FMLP-N-formyl-methionyl-leucyl-phenylalanine;PMNs- Polymorphonuclear cells.

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CONFLICT OF INTEREST

Conflict of interest declared none.

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