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Review

Recent Prospect of Compounds Derived from Marine Macroalgae for Medicinal Application of Anti-Inflammation for Chemoprevention of Cancer

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Abstract Although marine living organism contains a numerious number of compounds, it is difficult to collect these compounds in a large scale for medicinal application. However, in recent years, several bioactive compounds isolated from marine macroalgae have been proved to be able to provide potential sources for development of medicinal products because they can be obtained in large amount from marine. A number of studies have reported a variety of effects of marine macroalgae but a few anti-inflammatory activity of marine macroalgae have recently been published. Herein, we reviewed novel anti-inflammatory compounds recently isolated from marine brown algae, green algae and red algae. From this survey, in particular, some compounds contained in edible macroalgae exert anti-inflammatory effects with inhibition on cyclooxygenase-2 (COX-2), inducible nitric oxide synthase(iNOS) and matrix metalloproteinases (MMPs) activity regulated by nuclear factor-kappa B transcription factor that play a key role in cancer as well as inflammation, demonstrating to be able to potentially apply to development of anti-inflammatory agent for chemoprevention of cancer. Furthermore, some macroalgae and their compounds with both excellent anti-inflammatory activity and very low toxicity can select a potential candidates capable of preventing or treating several chronic inflammation such as colitis, hepatitis and gastritis, leading to cancer.

Key words : Anti-inflammatory; COX-2; iNOS; NF-kB; MMPs; Macroalgae

Introduction

Inflammation is largely classified into acute inflammation and chronic inflammation which are a kind of immune response expressed in body against biological infection such as bacteria, fungi and protozoa, exposure of various chemical agents or physical injury. It is involved in a wide variety of physiological as well as pathological processes of which symptom is accompanied by redness, heat, swelling and pain that can arise when an exogenous agent penetrates into body or when the immune system attacks its own tissue. First of all, acute inflammation is a short-term normal response that usually leads to tissue repair by leukocytes such as macroalgaes, neutrophils and eosinophils recruited into the damaged region, removing the cause of inflammation by production of a number of inflammatory mediators. However, if acute inflammation is not repaired, it eventually leads to chronic inflammation, giving own tissue damage [10]. Therefore, chronic inflammation is a long-term pathological response that involves tissue destruction due to the incompletion of tissue repair. Furthermore, it is well known that dysregulation of immune response can lead to chronic inflammatory diseases and pharmacological intervention is necessary to attenuate cellular inflammatory pathways. Such prolonged inflammation ultimately results in several chronic diseases, such as periodontal disease, hepatitis, arthritis, gastritis, colitis, atherosclerosis. In addition, it is now accepted that chronic inflammation is a major underlying condition of many age-related diseases, such as atherosclerosis, arthritis, cancer, diabetes, osteopo-

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rosis, dementia, vascular diseases, obesity and metabolic syndrome [8].

The most important factor in chronic inflammation has been known to be the nuclear factor-kappa B (NF-kB) transcription factor that plays a critical role in regulating both innate and adaptive immune responses [13]. It modulates inflammatory response through regulation of genes encoding pro-inflammatory cytokines, adhesion molecules, COX-2 and iNOS [3]. COX-2 has been known as an inducible enzyme with carcinogenic properties that is active within inflamed and malignant tissues. Several mechanisms of COX-2-mediated intestinal carcinogenesis have been reported to include inhibition of apoptosis, modulation of cellular adhesion and motility, promotion of angiogenesis, and immunosuppression [34]. In particular, there is also strong epidemiological evidence implicating COX-2 in the pathogenesis of a number of epithelial malignancies including gastric and colorectal cancer. Inhibitors of the enzyme are associated with a reduction of up to 50% in the morbidity and mortality of colorectal cancer [26]. Among the most potent inducers of COX-2 are the key proinflammatory cytokines IL-1α, IL-1β, and TNF-α. Accumulated data strongly suggest that continuous upregulation of several pro-inflammatory mediators such as TNF-a, IL-1 β, IL-6, COX-2 and iNOS are induced during the aging process due to an age-related redox imbalance that activates many pro-inflammatory signaling pathways, including the NF-kB signaling pathway. Current approaches to the treatment of inflammation rely on the inhibition of pro-inflammatory mediator production. In particular, COX-2, the key inducible enzyme responsible for producing prostanoids, and NF-*k*B can be attractive targets for developing anti-inflammatory medicines. Eicosanoids are especially key mediators of pain, fever, and inflammation. Hence, COX enzymes are the targets for common painkillers of the nonsteroidal anti-inflammatory drug (NSAID) class. Inhibitors that are selective for COX-2 have also been developed as anti-inflammatory agents, with the goal of minimizing the gastrointestinal complications associated with traditional NSAIDs that are among the most widely prescribed drug for treatment of many inflammatory diseases. These classical NSAIDs, such as aspirin, ibuprofen and indomethacin, markedly reduced gastric potential difference, suggesting disruption of the mucosal barrier. However, their major disadvantage is the high incidence of gastric, renal and hepatic adverse effects caused by the inhibition of prostaglandin synthesis. In recent years, anti-inflammatory agents have been focused on selective inhibitors of COX-2 without influencing the activity of constitutive COX-1. Selective inhibitors of the inducible isoform of COX-2 have been developed that should inhibit inflammatory PGs produced by the COX-2 enzyme, while sparing constitutive COX-1 produced PGs in the stomach [9]. 0Experimental and clinical results indicate that these drugs offer some advantages over the available NSAIDs, which either do not discriminate between the two COX isoforms or are actually selective COX-1 inhibitors. Recent data, however, suggest that COX-2 might also be necessary for the protection of the stomach while COX-1 might also be involved in the inflammation process [33]. 0In recent years, it has been reported that chronic inflammation is associated with an increased risk of malignant transformation. In particular, DNA mutation indirectly induced by these reactive intermediates can be a major cause of malignant transformation and age-related diseases. In another aspect, it was found that inflammation is involved in wound healing progression which trigers recruitment of leukocytes such as neutrophil, monocytes into skin injury. In addition, COX-2 inhibition might decrease scar collagen deposition after cutaneous injury[29].

On the other hand, transforming growth factors-β in wound healing is also secreted by platelets, fibroblasts and macroalgaes within the injury and are thought to act as attractants or inhibitors of keratinocyte, fibroblast and inflammatory cell migration, in up-regulation of collagen synthesis and modulation of matrix turnover via effects on MMPs and their inhibitors [35]. The MMPs are a family of secreted or transmembrane zinc-endopeptidases [22] that are capable of digesting extracellular matrix (ECM), such as fibrillar and non-fibrillar collagens, fibronectin, laminin, elastin and basement membrane glycoproteins under physiological conditions [5]. MMPs play an important role not only in physiologic degradation of ECM mediating tissue morohogenesis, tissue repair, and angiogenesis but also in pathologic conditions characterized by excessive degradation of ECM such as chronic inflammation, wrinkle formation, arthritis, osteoporosis, periodontal disease, tumor invasion and metastasis. Direct evidence for the

involvement of distinct MMPs in chronic inflammation has been revealed by many reports that MMP-8 is indeed associated with a wide range of inflammatory disorders, as well as cancer progression. The recent generation of MMP-8 deficient mice has allowed researchers to directly test the role of MMP-8 in a wide range of pathological conditions, which has strengthened the idea that MMP-8 is a central mediator in both acute and chronic inflammation [12].

However, despite the last decades of effect, there is no safe and effective antiinflammatory agent that can selectively inhibit COX-2 activity and treat chronic inflammation. Although studies on the anti-inflammatory mechanisms of a few candidates were extensively performed, a variety number of novel bioactive compounds remained unsolved. Therefore, in this review we intend to highlight natural bioactive compounds derived marine algae that are edible as traditional foods and show antiinflammatory activity. Marine algae are potentially abundant sources of highly bioactive secondary metabolites that might be available for the development of new pharmaceutical agents. In recent years, the study for marine natural product has yielded a considerable number of drug candidates. In particular marine algae have been recognized to provide chemical and pharmacological novelty and diversity. The current application of chemical compounds isolated from diverse classes of algae is enormous. Focusing on bioproducts, recent trends in drug research from natural sources suggest that algae are a promising group to furnish novel biochemically active substances. Several substantial reports regarding their anti-inflammatory effect is described below.

Anti-inflammatory effect of algae

Effect of brown algae on anti-inflammation

Although a number of studies have widely investigated the effects of marine algae, a few anti-inflammatory activity have recently been published. Although the anti-inflammatory effects of marine algae have been rarely reported, in recent years the data regarding them have been accumulating. Ryu et al. (2009) proposed that the inhibition of iNOS, COX-2 and MMP-1, MMP-3 and MMP-13 by dieckol and 1-(3-,5-dihydroxyphenoxy)-7-(2-,4-,6-trihydroxyphenoxy) 2,4,9-trihydroxydibenzo-1,4,-dioxin derived from *Ecklonia cava*, were resulted from mitogen-activated protein kinase (MAPK) such as c-Jun N-terminal kinase (JNK) and p38 mediated down-regulation rather than extracellular signal-regulated kinase (ERK) in human osteosarcoma (MG-63 cell line), providing a possibility that they have therapeutic potential for treatment of chronic inflammation such as arthritis [30]. In addition, potential anti-inflammatory effect of fucoxanthin isolated from *Myagropsis myagroides* was assessed via inhibitory effect of nitric oxide (NO) production in lipopolysaccharide (LPS) induced RAW 264.7 macroalgae [14]. Fucoxanthin significantly inhibited the NO production, it slightly reduced the prostaglandin E2 (PGE2) production. The iNOS and COX-2 protein expressions as well as their gene expression were inhibited by fucoxanthin, suggesting that fucoxanthin may be a useful for therapeutic approach for the various inflammatory diseases. Sugiura et al. (2009) demonstrated that anti-allergic effect of eckol, 6,60-bieckol, 6,80-bieckol, and phlorofucofuroeckol-B derived from an edible brown alga, Eisenia arborea, were exerted by anti-degranulation activity and inhibitory effects on enzymatic activities involved in eicosanoid (leukotoriene and prostaglandin) synthesis in RBL cells or KU812 cells, providing an evidence for their anti-allergic effect [32]. Furthermore, Polyunsaturated fatty acid-derived monoglycerides from *Sargassum Sagamianum* , 1-octadecatetraenoyl glycerol, exhibited a significant inhibition of phospholipase A2 and COX-2, indicating that it may be a good potential lead compound for treatment of inflammation [6]. In addition, polysaccharides of edible algae, *Sargassum latifolium*, was found to contain cancer chemopreventive fractions, since they had tumor anti- initiating activity via their protective modulation of carcinogen metabolism, and tumor anti-promoting activity via their anti-inflammatory activity [11]. Kang, et al. (2008) reported that the present investigation demonstrated that extracts of the brown seaweeds *Sargassum fulvellum* and *Sargassum thunbergii* have potent anti-edema activity, without any serious toxic effect at moderate doses. These findings reinforce the claims of the health care industry and indigenous medicine that those seaweeds can be used as remedies for inflammation related symptoms [18]. In addition, *Ecklonia cava* was found to suppresses the induction of cytokines by LPS, as well as iNOS and COX-2 expression, by blocking NF-kB and MAPK activation, providing mechanistic insights into the its an-

ti-inflammatory and neuroprotective action in BV2 microglia [22]. Furthermore, MMP inhibitors have been identified as potential therapeutic candidates for metastasis, arthritis, chronic inflammation and wrinkle formation. For the first time our group found inhibitory effects of phlorotannins in brown algae, *Ecklonia cava* on MMP activities in cultured human cell lines, anticipating its potential use as a safe MMP inhibitor for chronic inflammation [21]. On the other hand, ethanolic extract of *Ishige okamurae* was effective in inhibiting the production of inflammatory mediators, such as tumor necrosis factor-α, interleukin-1 β, interleukin-6 and prostaglandin E2, in RAW264.7 cells stimulated by lipopolysaccharide, compared with dexamethasone and aspirin used as positive control. Its mechanism of action includes anti-inflammation exerted through inactivation of NF-κB transcription factor in macroalgae [20]. In addition, a methoxylated fatty acid purified from Ishige okamurae inhibited phospholipase A activity in vitro and has potent anti-inflammatory activity in vivo [7].

Effect of green algae on anti-inflammation

Recent trends in drug research from natural sources have shown that algae are promising organisms for the development of novel biochemical active compounds. Among the

different species of green algae with remarkable biochemical activity, the marine green alga, *Ulva lactuca*, was shown to contain 3-O-beta-D glucopyranosyl-stigmasta-5,25-dien. The topical antiinflammatory activity of this compound was examined using the mouse ear oedema assay as an experimental model of topical inflammation [2]. Park, et al. (2008) reported that the lipid extract from a blue-green alga, *Nostoc commune*, can modulate proinflammatory gene expression in RAW 264.7 macroalgaes. It was found that the fatty acid mixture from this alga significantly reduced RNA abundance of TNF-α and COX-2, lipid extract can repress the expression of proinflammatory genes in RAW 264.7 macroalgaes, at least in part, by inhibiting the activation of NF-κB pathway [27]. In another study, *Capsosiphon fulvescens* known as a green alga and nutrient-dense food source was demonstrated to contain polysaccharide that exerts antitumor effect in gastric cancer cells. In this report, the protective effect of polysaccharide from this alga against alcohol-induced gastric injury in rats and adenocarcinoma cells was investigated. In vivo assay revealed stomach damage in rats treated with alcohol alone its treatment reduced the expressions of COX-2 and the inducible form of nitric oxide, proteins related to ulcers. These results suggest that it could help protect against alcoholinduced peptic ulcers [15]. C-Phycocyanin (C-PC) is one of the major biliproteins of *Spirulina platensis*, a blue green algae, with antioxidant and radical scavenging properties. It was also reported to exhibit anti-inflammatory and anti-cancer properties. Previous report demonstrated that C-PC selectively inhibits COX-2, an inducible isoform that is upregulated during inflammation and cancer. These effects of CPC on RAW 264.7 cells was reported to exert due to the reduced PGE2 levels as a result of COX-2 inhibition [28]. Marine algae have been utilized in food products as well as in medicine products for a variety of purposes. Jin et al. (2006) described that inflammatory processes are associated with the pathophysiology of Alzheimer's disease (AD), and the treatment of AD using anti-inflammatory agents slows the progress of AD. In their study, the neuroprotective effects of methanol extracts of *Ulva conglobata* on glutamate-induced neurotoxicity in the murine hippocampal HT22 cell line and the anti-inflammatory effects on interferon gamma-induced microglial activation in BV2 cells were examined. *U. conglobata* methanol extract treatments almost completely suppressed the expression of the proinflammatory enzyme COX-2 and iNOS. They suggest that *U. conglobata* possesses therapeutic potential for combating neurodegenerative diseases associated with neuroinflammation [16].

Effect of red algae on anti-inflammation

The antioxidant and anti-inflammatory properties of *Neorhodomela aculeate* a marine red alga,were investigated with neuronal and microglial cells. It was found that extracts of *N. aculeata* have potent neuroprotective effects on glutamate-induced neurotoxicity and inhibited reactive oxygen species generation in the murine hippocampal HT22 cell line. Also, extracts of *N. aculeata* inhibited H2O2-induced lipid peroxidation in rat brain homogenates. The properties of the extract as an anti-inflammatory agent were exhibited through reduction of iNOS that consequently resulted in the reduction of nitric oxide. These results confirm that the marine red alga *N. aculeata* could be considered as a potential

source for reducing reactive oxygen species and inflammation related to neurological diseases [24]. Lee, et al. (2009) reported that the ingredients of *Gracilaria verrucosa* having anti-oxidant and anti-cancer properties operate through an unknown mechanism. They isolated two enone fatty acids from *G. verrucosa* and investigated their molecular mechanism in LPS-stimulated RAW264.7 cells. They found that the two compounds inhibited the production of inflammatory markers (nitric oxide, TNF-alpha, and IL-6) in a dose-dependent manner. Their mechanism of action is that they can suppress NF-kB activity by interfering with nuclear translocation of NF-kB and suppressed JAK/STAT (p-STAT1) signaling [23]. In previous study, sulfated-polysaccharides was suggested to be exploite as antithrombotic, anticoagulant agents and immunostimulants. The agglutinin from the red marine alga *Hypnea cervicornis* was tested for antiinfalmmatory activity using model of inflammation using carrageenan-induced paw edema. The agglutinin showed important antinociceptive and anti-inflammatory activity via interaction with the lectin carbohydrate-binding site [4]. In another study, a mineral-rich extract derived from the red marine algae *Lithothamnion calcareum* used as a dietary supplement was examined for chemoprevention against colon polyp formation in C57bl/6 mice. Autopsies revealed that colon polyps was completely inhibited in animals treated with mineral-rich extract from this alga. In addition to the grossly visible polyps, areas of hyperplasia in the colonic mucosa and inflammatory foci throughout the gastrointestinal tract were observed histologically in animals on the high-fat diet. However, they were significantly reduced in animals on the low-fat diet and animals on the extract-supplemented group, suggesting that the mineral-rich algae extract may provide a novel approach to chemoprevention in the colon [1]. *Porphyra dentat*a, a red edible seaweed, has long been used worldwide in folk medicine for the treatment of inflammatory diseases such as hypersensitivity, lymphadenitis, bronchitis. The anti-inflammatory role of *Porphyra dentata* crude extract was investigated for their effect on the nitric oxide/iNOS transcription pathway in macroalgae RAW 264.7 cells. Phenolic compounds such as catechol, rutin and hesperidin were identified in the crude extract of *Porphyra dentata*. Both the crude extract and the phenolic compounds exhibited inhibitory effect on production of NO in LPS-stimulated RAW264.7 cells. In particular, catechol was a more potent suppressor of the up-regulation of iNOS promoter and NF-kB enhancer than rutin and yet, hesperidin alone failed to inhibit either activity. These results provide a evidence that catechol and rutin, but not hesperidin, are primary bioactive phenolic compounds in the crude extract to suppress NO production in LPS-stimulated macroalgaes via NF-kB-dependent iNOS gene transcription, leading to anti-inflammatory use [19]. Researchers see algae as a promising tool to discover both efficient and safe agents for pain therapy. The anti-inflammatory activities of lectin from the marine alga *Pterocladiella capillacea* lectin. It was reported that leukocyte migration was induced by carrageenan (500m g/cavity) in male Wistar rats and that this alga group (8.1 mg/kg, i.v.) significantly reduced neutrophil migration by 84%, as compared to untreated animals, suggesting inhibition of inflammatory mediators. Their results indicated that this alga has peripheral actions with both anti-inflammatory and antinociceptive properties [25]. Neuroinflammation with prolonged microglial activation leads to increased levels of pro-inflammatory mediators and subsequently contributes to neuronal dysfunction and neuronal loss. Therefore, pharmacological suppression of neuroinflammation would theoretically slow the progression of neurodegenerative disease. Lim, etal. (2010) investigated the anti-inflammatory effects and possible mechanisms of isodojaponin D (19-hydroxy-1α,6-diacetoxy-6,7-seco-ent-kaur-16-en-15-one-7,20-olide), a new diterpene isolated from *Isodon japonicus* against lipopolysaccharide (LPS)-induced microglial activation in BV2 cells. It was observed that pretreatment with isodojaponin D (5 and 10 μg/ml) prior to treatment with LPS significantly decreased LPS-induced production of COX-2 and iNOS in a dose-dependent manner. In addition, LPS-induced pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, were also decreased by pretreatment with isodojaponin D. This effect was accompanied by a decrease in translocations of NF-κB from the cytoplasm to the nucleus and by a decrease in IκB degradation. In addition, pretreatment with isodojaponin D significantly attenuated LPS-induced mitogen-activated protein kinase activation. These results revealed that isodojaponin D suppressed LPS induced microglial activation and production of pro-inflammatory mediators by inhibition of the NF-κB signaling pathway and phosphorylation of MAPKs, suggesting that isodojaponin D

could play a beneficial role in treatment of neurodegenerative disease [35].

Conclusions

In recent years, although marine source such as sponge contains a numerious number of compounds containing a variety of anti-inflammatory compounds derived from marine resources such as astaxanthin, bolinaquinone, cacospongionolide B, clathriol B, conicamin, cycloamphilectene 2, elisabethadione, plakohypaphorine, pourewic acid A and so on, it is difficult to collect these compounds in a large scale for industrial application. However, in recent years, several bioactive compounds isolated from marine macroalgae have been proved to be able to provide potential sources for development of medicinal products. because they can be obtained in large amount from marine. Although a number of studies have widely investigated the effects of marine macroalgae, a few anti-inflammatory activity of marine macroalgae that we have focused on have recently been published. Among novel anti-inflammatory compounds recently isolated from marine brown algae, green algae and red algae , some compounds contained edible macroalgae exert anti-inflammatory effects with COX-2, iNOS and MMPs activities up-regulated by NF-*k*B transcription factor that play a key role in inflammation, demonstrating to be able to potentially apply to the development of anti-cancer agent as well as anti-inflammatory agent. However, the majority of marine bioactive compounds discussed in this review has not been clarified in view of their clinical pharmacological aspects so far. Therefore, in addition to isolation of new potential compounds with anti-inflammatory activity, it is required to elucidate mechanism of pharmacological action of effective compounds against cell lines or animal model to develop these compounds as novel anti-inflammatory agents. Furthermore, some macroalgae and their compounds with both excellent anti-inflammatory activity and very low toxicity can select a potential candidates capable of preventing or treating several chronic inflammation such as colitis, hepatitis and gastritis, leading to cancer.

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