CHAPTER 10

Phlorotannins and Fucoidans from Marine Macroalgae as Matrix Metalloproteinase Inhibitory Substances and Their possible Application as Medicinal Foods

Se-Kwon Kim,[*,†,1] **Noel Vinay Thomas,**[*] and **Xifeng Li**[†,‡]

Contents

Abstract

Metalloproteinases especially matrix metalloproteinases are a group of endopeptidases that contribute for the extracellular matrix degradation, and several tissue remodeling processes. Improper regulation of these endopeptidases could lead to several severe pathological problems that include cardiac, cartilage, and cancer-related diseases. Until now, many synthetic matrix metalloproteinase inhibitory substances (MMPIs) have been reported; however, many of them could not make to the final clinical trials.

* Marine Biochemistry Laboratory, Department of Chemistry, Pukyong National University, Busan, Republic of Korea
† Marine Bioprocess Research Center, Pukyong National University, Busan, Republic of Korea
‡ Department of Chemistry, College of Science, Yanbian University, Jilin, PR China
1 Corresponding author: Se-Kwon Kim, *E-mail address:* sknkim@pknu.ac.kr

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Hence, the emphasis on screening of MMPIs from different natural resources has gained much importance and marine resources are one among them. As marine organisms have been contributing with several biologically active compounds that have profound applications in nutraceuticals, cosmeceuticals, and pharmaceuticals; in this chapter, an attempt has been made to discuss the various MMPIs from edible seaweeds, which could be considered as medicinal foods.

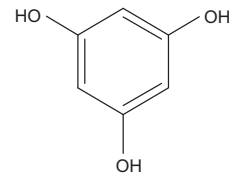
I. INTRODUCTION

Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases that degrade the extracellular matrix, and this is considered as a general remodeling process that enables several physiological processes like wound healing, bone resorption, uterine involution, and organogenesis as well as pathologic conditions including inflammatory, vascular, and autoimmune disorders, and carcinogenesis (Egeblad and Werb, 2002; Lee and Murphy, 2004). It is reported that MMPs are involved in tumor invasion, angiogenesis, metastasis, transformation of cancer cells, signal transduction, and apoptosis (Overall and López-Otín, 2002) that makes them an ideal target for the treatment of cancer-related disorders. Normally, the phenomena of intercellular regulation and cell matrix adhesion are regulated in a controlled fashion; however, superior expressions of MMPs deregulate this event and result in various kinds of human cancers (Bourboulia and Stetler-Stevenson, 2010). Tissue inhibitors of metalloproteinase, commonly known as TIMPs, are naturally occurring inhibitors for the overexpression of MMPs and are known to prevent the proteolytic degradation. Factors like solubility and interaction of TIMPs with pro-MMPs do determine the inhibitory activity of TIMPs (Lambert *et al.*, 2004). Several pathological responses associated with MMPs have made them as therapeutic targets for the better management of human cancers. Till now, many synthetic MMPIs have been reported. Synthetic drugs like Batimastat (BB-94) and Marimastat (BB-516) have been successful in lowering the expression of MMPs. However, improper metabolism, low oral bioavailability, poor solubility, side effects like musculoskeletal pain and inflammation, complications, and the risk of increased drug toxicity is still a big challenge (Coussens *et al.*, 2002; Thomas and Kim, 2010). Because of these shortcomings of the synthetic MMPIs, researchers are screening natural resources for the screening of MMPIs and few research groups have been successful in reporting natural MMPIs from terrestrial organisms (Ha *et al.*, 2004; Seo *et al.*, 2005). However, the diversified environment in sea water enables the marine organisms with unique abilities for their survival and makes them ideal choice for the screening of biologically active compounds.

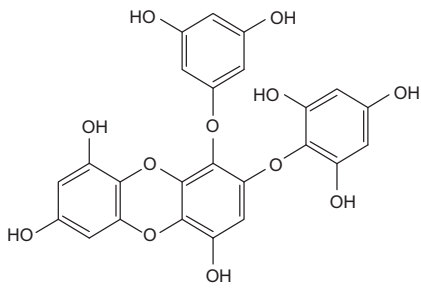
Seaweeds or marine macroalgae are considered as dietary components and also as alternative medicine in Asian countries like Japan, Korea, and China (Ali *et al.*, 2000). In recent times, isolation and characterization of the biologically important compounds have gained lot of attention from various research groups across the world. Marine brown algae have been extensively studied for their biologically active components that majorly include polyphenolic derivatives called phlorotannins and polysaccharides like fucoidans, alginic acid, etc. In this chapter, we would be discussing the role of phlorotannins and polysaccharides from marine macroalgae as potential MMPIs.

II. MARINE ALGAL PHLOROTANNINS AS POTENTIAL MMPIs

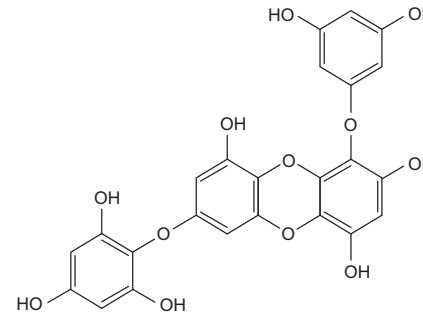
It is a well-understood fact that marine flora harbors a wide range of biologically active compounds that are reported to have an outstanding prospective in the medicinal, nutraceutical, and cosmeceutical applications. Natural metabolites obtained from marine seaweeds prove to be abundant resources with chemical diversity, and among them, phlorotannins are studied most for their biological activities. These phlorotannins (Fig. 10.1) are derived from tannins and are composed of several phloroglucinol units linked to each other in different ways and mostly



Phloroglucinol

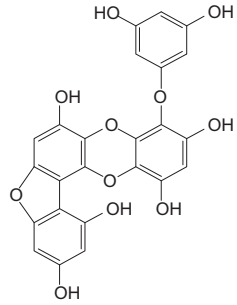


2-Phloroeckol

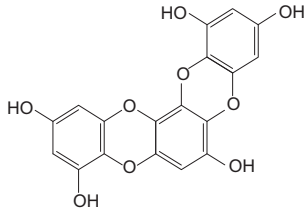


7-Phloroeckol

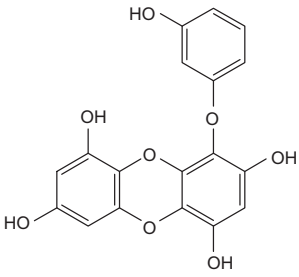
FIGURE 10.1 (Continued)



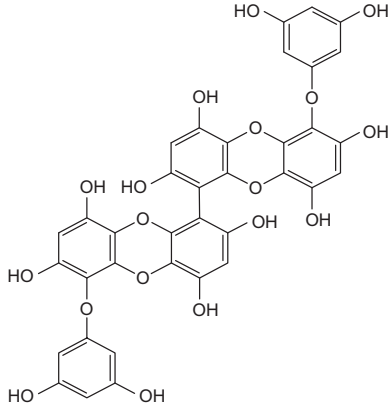
Fucofuroeckol-A



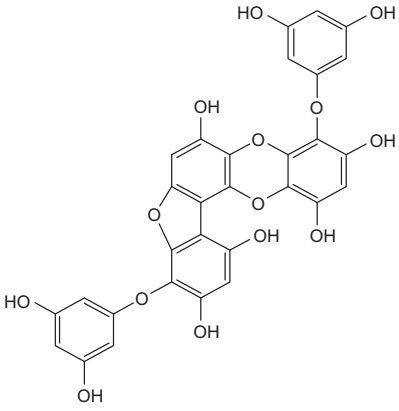
Dioxynodehydroeckol



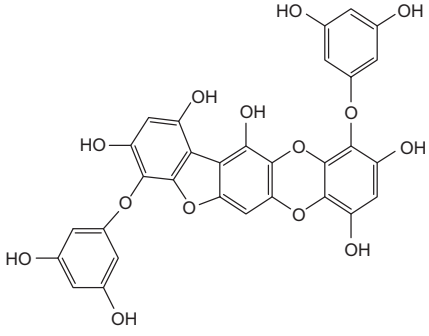
Eckol



6,6′-Bieckol



Phlorofucofuroeckol-A



Phlorofucofuroeckol-B

FIGURE 10.1 (Continued)

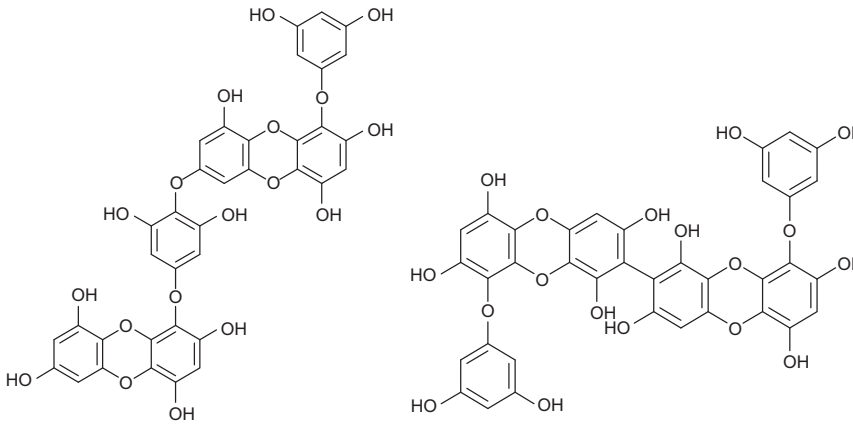


FIGURE 10.1 Phlorotannins derived from brown seaweeds and their chemical structures.

distributed in marine brown algae (Singh and Bharate, 2006). It is suggested that formation of phlorotannins is by polymerization of phloroglucinol (1,3,5-trihydroxybenzene) monomer units and biosynthesized through the acetate–malonate pathway, also known as polyketide pathway. Usually, their molecular sizes range from 126 to 650 kDa (Ragan and Glombitza, 1986). Recent studies recommend that the polyphenolic compounds derived from marine algae have preventive properties against human diseases including cancer, coronary heart diseases, and other allergies (Shibata *et al.*, 2003), hence suggesting the brown algae as potential medicinal food.

Based on substrate specificity, the MMPs are categorized into three major functional groups. The main three groups include interstitial collagenases that have affinities toward collagen types I, II, and III (MMP-1, MMP-8, and MMP-13); the stromelysins with specificity for laminin, fibronectin, and proteoglycans (MMP-3, MMP-10, and MMP-11); and the gelatinases that effectively cleave type IV and type V collagen (MMP-2 and MMP-9; Nelson *et al.*, 2000). Two phlorotannins namely dieckol and 1-(3′,5′-dihydroxyphenoxy)-7-(2′,4′,6′-trihydroxyphenoxy) 2,4,9-trihydroxydibenzo-1,4,-dioxin isolated from the methanol extract of marine brown alga, *Ecklonia cava*, have been reported to suppress both the protein and gene expression levels of MMP-1, MMP-3, and MMP-13 in human osteosarcoma cells (MG-63). This *in vitro* study also reports that these phlorotannins were able to promote osteosarcoma differentiation by increasing alkaline phosphatase (ALP) activity,

mineralization, total protein, and collagen synthesis (Ryu *et al.*, 2009b). Similarly, dieckol and eckol isolated from *Ecklonia stolonifera* have inhibited the expression of MMP-1 in human dermal fibroblast (HDF) cell, *in vitro* (Joe *et al.*, 2006). More precisely, this investigation suggested that these phlorotannins interfere with the expressions of NF-κB and activator protein-1 (AP-1) which in turn enhances the MMP-1 expression that leads to skin-related damages. Hence, brown algae can be recommended as foods with medicinal values that can aid for skin care.

Skin wrinkling is normally attributed by the reactive oxygen species (ROS) which is caused by the oxidative stress. ROS stimulates mitogen-activated protein kinases that phosphorylate transcription factor AP-1, which in turn results in upregulation of MMPs that contribute for the degradation of skin collagen ultimately leading to skin ageing (Fisher *et al.*, 1996; Rittié and Fisher, 2002). The gelatinases that include MMP-2 and MMP-9 promote UV-induced skin damage. It is reported that sun-damaged skin shows significantly elevated levels of active gelatinases (MMP-2 and MMP-9) than intrinsically aged skin (Chung *et al.*, 2001). *In vitro* studies on methanol extract from marine alga *Corallina pilulifera* (CPM) have revealed that CPM has the ability to prevent UV-induced oxidative stress and also the expressions of MMP-2 and MMP-9 in HDF cells. This clearly suggests the role of phenolic compounds from marine algae as potential MMPIs (Ryu *et al.*, 2009a). As it is evident that unregulated expression of MMPs leads to the photoaging, many research groups are emphasizing their research goals to check the ability of marine-derived phlorotannins as potential antiphotoaging agents. Moreover, the ROS that includes hydrogen peroxide, hydroxyl radical, and superoxide anion is involved in metabolic diseases, especially chronic inflammation. In chronic inflammation, proinflammatory cytokines induce MMPs that degrade the extracellular matrix and contribute for several inflammatory disorders. In this process of screening the medicinally valuable agents from marine seaweeds, phloroglucinol, a monomer of phlorotannins, is reported to exhibit anti-inflammatory effect in addition to free radical scavenging activity. This *in vitro* study has revealed the MMP-2 and MMP-9 inhibitory activities in HT1080 cells, thus suggesting the potentiality of phloroglucinol as an antimetastatic compound. Moreover, the phloroglucinol has exhibited anti-inflammatory activity by expression levels of TNF-α, IL-1β, IL-6, and PGE_2 in macrophages RAW264.7 (Kim and Kim, 2010). These *in vitro* studies bring front the scientific proof that phloroglucinol from marine algae can be recommended as a medicinal agent to reduce the risk of metastasis and inflammation-related diseases. On the other hand, reports suggest that some other brown alga contain higher amount of phloroglucinol (Koivikko *et al.*, 2005) and have exhibited several medicinally beneficial effects *in vitro*. Hence, members of brown seaweeds can be recommended as medicinal foods because of

the abundant presence of polyphenolic compounds that aids for the betterment of human health.

The species *Ecklonia* and *Eisenia* are the mostly studied brown algae for the biological activities associated with phlorotannins. The *E. cava* extract has the capability to reduce the expression of MMP-2 and MMP-9. An *in vitro* study on the effect of *E. cava* extract in HDF cells (HT1080) has revealed that the extract which was rich in phlorotannins has attenuated the expression of MMP-2 and MMP-9 expression (Kim *et al.*, 2006). Interestingly, this *in vitro* study has revealed that the phlorotannis did not exhibit any cytotoxicity on the cells and has the MMP inhibitory effect almost same to that of doxycyclin (a commercial MMP inhibitor). Similarly, phlorotannins namely fucofuroeckol-A and eckol that are derived from *Eisenia bicyclis* had shown MMP-2 and MMP-9 inhibitory activities in HT1080 cells. In this study, it has been suggested that fucofuroeckol-A and eckol exhibited a significant inhibitory activity on the NF-κB expression and also they had a considerable inhibitory effect on AP-1 expression, thus inhibiting the expression of MMP-2 and MMP-9 via blocking the transcription of both NF-κB and AP-1 (Lee, 2010). As the investigations suggest that MMP-2 (Gelatinase-A) and MMP-9 (Gelatinase-B) can degrade type IV collagen of base membranes and are known to play a crucial role in cancer invasion such as oral carcinoma and other cancers (Ikebe *et al.*, 1999) and that these enzymes play a major role in cancer metastasis (Nagase *et al.*, 1998), the MMP downregulation effect of phlorotannins and polyphenolic compounds from marine brown algae stands more promising and recommending them as potential medicinal foods to combat metastasis.

The phlorotannins eckol and dieckol that were first isolated from *Ecklonia* species possess oligomeric polyphenol of phloroglucinol unit. Dieckol from marine brown alga, *E. cava*, has been reported to suppress LPS-induced production of nitric oxide (NO) and prostaglandin E_2 (PGE_2) and expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in murine BV2 microglia, thus establishing dieckol as a potent anti-inflammatory and neuroprotective agent (Jung *et al.*, 2009). A detailed account of the various biological activities including free radical scavenging activity of phlorotannins from *Ecklonia* species has been reported earlier.

III. MARINE ALGAL FUCOIDANS AS POTENTIAL MMPIs

Marine algae are reported to produce different polysaccharides including alginates, laminarans, and fucoidans. They usually contain large proportions of L-fucose and sulfate, together with minor amounts of other sugars such as xylose, galactose, mannose, and glucuronic acid. These algal

polysaccharides have been attributed with many biological activities such as anticoagulant, antithrombotic, antitumoral, and antiviral activities. Especially fucoidans from marine algae have been reported to exhibit outstanding biological activities that aid for human health. Fucoidans (Fig. 10.2) are sulfated polysaccharides that are exclusively found in seaweeds in their cell wall. This polysaccharide ingredient is composed of polymer of α1 → 3-linked 1-fucose with sulfate groups on some of the fucose residues at the four positions (Patankar *et al.*, 1993). Recently, fucoidan is being studied extensively due to potential antitumor, antiviral, anticomplement, and anti-inflammatory activities (Chizhov *et al.*, 1999). Brown algae-derived fucoidan has been reported to show strong inhibition ability on UVB-induced MMP-1 expression *in vitro*. In an investigation by Moon *et al.*, human skin fibroblast (HS68) cells were pretreated by various concentrations of fucoidan and then subjected to UVB irradiation (100 mJ/cm^2). As it is known that UVB irradiation induces the production of MMPs by activating cellular signaling transduction pathways, which are responsible for the degradation or synthesis inhibition of collagenous extracellular matrix in connective tissues, causing skin photoaging. Their results have suggested that fucoidan from algae has successfully inhibited the expression of MMP-1 by the suppression of extracellular signal-regulated kinase (ERK). Moreover, in fucoidan-treated cells, the expression of MMP-1 mRNA has been significantly reduced (Moon *et al.*, 2008). As brown edible algae are considered as dietary food stuff, the consumption of brown algae that are rich in fucoidan could be beneficial in reducing the risk of MMP-related diseases.

Similarly, another research group reported the MMP inhibitory effect of a 16-kDa fucoidan fraction from seaweeds on the parameters involved

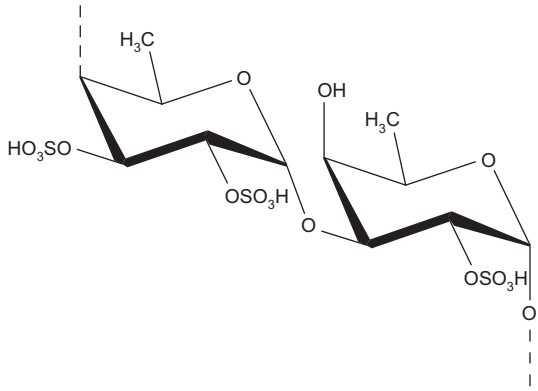


FIGURE 10.2 Chemical structure of fucoidan unit.

in connective tissue breakdown. It was observed that this 16 kDa fucoidan was able to successfully inhibit the gelatinase A secretion and stromelysin 1 induction by interleukin-1β on dermal fibroblasts *in vitro*. In addition, *ex vivo* studies using the tissue sections of human skin have revealed that this polysaccharide was able to minimize human leukocyte elastase activity resulting in the protection of human skin elastic fiber network against the enzymatic proteolysis due to this serine proteinase (Senni *et al.*, 2006). These findings clearly suggest the potential role of seaweed fucoidans in reducing the risk of some inflammatory pathologies that involve extracellular matrix degradation by MMPs. Usually, high molecular weight (HMW) fucoidans are known to bind to the growth factors, such as fibroblast growth factor (FGFs), and protect them from proteolysis (Belford *et al.*, 1993). The therapeutic ability of fucoidans thought to be associated with the fact that they can release the glycosaminoglycan-bound stromal-derived factor-1 (SDF-1) from its tissue storage sites. SDF-1 mobilizes medullary progenitors which could participate in angiogenesis with vascular endothelial growth factor (VEGF) and FGF (Salvucci *et al.*, 2002; Sellke *et al.*, 1996). A fraction of low molecular weight (LMW) fucoidan (7 ± 2 kDa) obtained by radical depolymerization of HMW extracts from brown seaweed have been reported to promote therapeutic revascularization in a rat model of critical hindlimb ischemia (Luyt *et al.*, 2003). Normally, MMP-9 plays an important role in both animal models of cerebral ischemia and human stroke. The expression of MMP-9 is elevated after cerebral ischemia which is involved in accelerating matrix degradation, disrupting the blood–brain barrier, increasing the infarct size, and relating to hemorrhagic transformation (Dong *et al.*, 2009). The therapeutic ability of seaweed fucoidans would be a best option in managing the MMP-associated cerebral ischemia.

Fucoidans isolated from *Costaria costata* have been reported to possess the MMP inhibition activities. *In vitro* study using the immortalized human keratinocyte (HaCaT) cell line pretreated with *C. costata*-derived fucoidans has shown a significant decrease in the UVB-induced MMP-1 expression. Moreover, fucoidan has significantly reduced the expression MMP-1 mRNA and inhibited UVB-induced MMP-1 promoter activity by 37.3%, 53.3%, and 58.5% at 0.01, 0.1, and 1 μg/mL, respectively, compared to UVB irradiation alone (Moon *et al.*, 2009). Fucoidan extracts from seaweed *Cladosiphon novae-caledoniae* Kylin (Mozuku) have reduced the cellular invasiveness in human fibrosarcoma HT1080 cells by suppressing the activity of MMP-2 and MMP-9. Further, it has been reported that these fucoidan extracts suppressed the expression and secretion of an angiogenesis factor, VEGF, thereby reporting the inhibitory effects on invasion and angiogenesis of tumor cells (Ye *et al.*, 2005). Another research group has reported that fucoidan exerts its antiproliferative action. *In vitro* studies on the cultured AGS human gastric adenocarcinoma cells treated

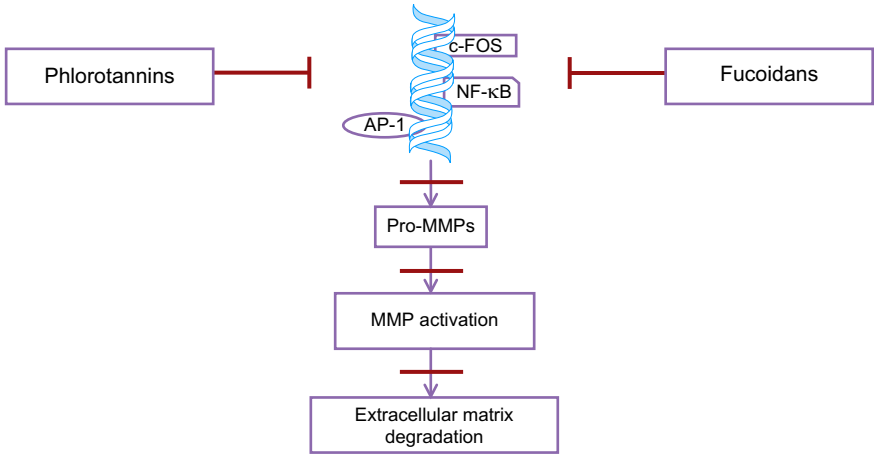


FIGURE 10.3 Generalized representation of the inhibitory effects of seaweed phlorotannins and fucoidans on MMP activity.

with fucoidans suggest that fucoidan effectively inhibits the growth of AGS cells by inducing autophagy, as well as apoptosis. They have also reported that the downregulation of antiapoptotic Bcl-2 and Bcl-xL expression, loss of mitochondrial membrane potential, activation of caspases, and concomitant degradation of poly-(ADP-ribose) polymerase protein are involved in the fucoidan-induced apoptosis (Park *et al.*, 2011). Thus, fucoidans can be of great potential in controlling the expressions of MMPs that regulate the cell proliferation and metastasis and hence can be better dietary supplements in managing cancers (Fig. 10.3).

IV. CONCLUSIONS AND FURTHER PROSPECTS

The recent scientific investigations have unleashed the prominent role of metalloproteinases in several human-related pathological conditions, and the drawbacks of the currently available synthetic MMPIs encourage the present day researchers to explore natural resources for effective MMPIs. Moreover, the shortcomings of synthetic MMPIs like nonspecific selectivity, improper metabolization, and undesirable side effects also demand the researchers to screen for the MMPIs from natural resources. Until now, many therapeutic compounds have been reported from terrestrial organisms. But, the oceans' flora and fauna are exposed to harsh environment and are equipped with variety biochemical responses to evade potential threats they encounter in marine locales. For performing such unique responses, the marine organisms produce unique biologically

active components that are structurally and functionally different from terrestrial organisms. Among these, phlorotannins and fucoidans are specifically found in the marine algae. And the above discussed *in vitro*, *in vivo* reports clearly suggest the effectiveness of phlorotannins and fucoidans from brown algae in proper downregulation of MMPs and related pathological effects. Moreover, as brown algae are considered as a dietary supplement, it could be recommended that consumption of these marine brown algae could be helpful in the proper management of imbalanced MMP expressions and thus can be considered as medicinal foods. Further, until now, majority of the phlorotannins and fucoidans reported were from the members of the species *Ecklonia* and *Eisenia*. Many more brown algal members have to be screened for novel phlorotannins and polysaccharide derivatives that can be recommended as potential MMPIs.

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