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Fucoidans as a natural bioactive ingredient for functional foods

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ABSTRACT

Functional food is considered to be any food or food component that provides health benefits beyond basic nutrition. Recently, a great deal of interest has been paid by the consumers towards natural bioactive compounds as functional ingredients in the diets due to their various health beneficial effects. Notably, marine resources have been recognized as rich sources of structurally diverse biologically active compounds with great application potential in marine functional foods. Among them, fucoidans have been found to possess various bioactivities including antioxidant, anti-inflammatory, anti-allergic, anti-tumor, anti-obesity, anti-coagulant, anti-viral, anti-hepatopathy, anti-uropathy, and anti-renalpathy effects. Hence, this contribution focuses on fucoidans derived from marine sources and presents a brief overview of their biological activities with health benefits.

Contents

1. Introduction . . . 17
2. Fucoidans: sources, molecular structure, and physiological properties . . . 17
   2.1. Sources . . . 17
   2.2. Molecular structure . . . 17
   2.3. Physiological properties. . . . 18
3. Biological activities of fucoidans . . . 18
   3.1. Anti-coagulant activity . . . 18
   3.2. Anti-viral activity . . . 19
   3.3. Anti-inflammatory activity . . . 20
   3.4. Anti-allergic activity . . . 21
   3.5. Antioxidant activity. . . . 21
   3.6. Anti-obesity activity . . . 22

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3.7. Anti-tumor activity . . . 22
3.8. Other biological activities of fucoidan . . . 22
4. Conclusion . . . 23
References . . . 23

1. Introduction

The food habits have been considered to be important factors associated with health status. Consumption of junk food has increased manifold, which has led to a number of diseases related to nutritional deficiencies (Manisha, Rohit, & Shubhini, 2010). Recently, consumers are understandably more interested in the potential benefits of nutritional support for disease control or prevention (Hardy, 2000). Thus, functional food is known to play important role in reducing health risks and improving health quality. Meanwhile, the capacity of some plant-derived foods to reduce the risk of chronic diseases has been associated, at least in part, to the occurrence of secondary metabolites that have been shown to exert a wide range of biological activities. In general, these metabolites have low potency as bioactive compounds when compared to pharmaceutical drugs, but since they are ingested regularly and in significant amounts as part of the diet, they may have a noticeable long-term physiological effect (Espín, García-Conesa, & Tomás-Barberán, 2007). Notably, these products are expected due to its medicinal synergy, safety, economical status, and fewer side effects than many drugs routinely prescribed in the treatment of certain symptoms (Raskin et al., 2002). Herein, a number of functional foods have been found from natural sources such as oats, soy, tomatoes, garlic, broccoli, citrus fruits, cranberry, royal jelly, tea, fish, and beef, among others (Hasler, 1998; Ramadan & Al-Ghamdi, 2012; Shao et al., 2009; Zhang et al., 2012).

Recently, a great deal of interest has been developed by consumers towards novel bioactive compounds as ingredients in functional foods from marine natural resources (Kim & Wijesekara, 2010; Pangestuti & Kim, 2011). It is well-known that the world's oceans, covering more than 70% of the earth's surface, provide a diverse living environment for invertebrates (Vignesh, Raja, & Arthur James, 2011). Marine organisms have evolved biochemical and physiological mechanisms that include the production of bioactive compounds for reproduction, communication, and protection against predation, infection, and competition (Halvorson, 1998). Thus, marine environment has been a rich source of both biological and chemical diversity. During the last decades, numerous novel compounds have been isolated from marine organisms and many of these compounds are potential for industrial development of functional foods and pharmaceuticals (Blunden, 2001; Blunt, Copp, Munro, Northcote, & Prinsep, 2006; Mayer, Rodriguez, Berlinck, & Fusetani, 2011). ~~Among them, fucoidans have been found due to their antioxidant, anti-inflammatory, anti-allergic, anti-tumor, anti-obesity, anti-coagulant, anti-viral, anti-hepatopathy, anti-uropathy, and anti-renalpathy effects (Li et al., 2008) (Table 1).~~ These special properties of fucoidans have supported it to be applied to functional foods for disease prevention and health promotion. Thus, this contribution provides a cursory account of fucoidans with their biological activities and health benefit effects.

2. Fucoidans: sources, molecular structure, and physiological properties

2.1. Sources

Fucoidans are a complex series of sulfated polysaccharides found widely in the cell walls of brown seaweeds. In recent years, different brown algae were analyzed for their content of fucoidans including *Pelvetia canaliculata* (Descamps et al., 2006), *Fucus vesiculosus* (Béress et al., 1993; Obluchinskaya & Minina, 2004), *F. evanescens* (Kuznetsova et al., 2003), *F. serratus* (Bilan, Grachev, Shashkov, Nifantiev, & Usov, 2006), *F. distichus* (Bilan et al., 2004), *Sargassum stenophyllum* (Duarte, Cardoso, Noseda, & Cerezo, 2001), *Ascophyllum nodosum* (Medcalf & Larsen, 1977), *Cladosiphon okamuranus* (Sakai, Ishizuka, Shimanaka, Ikai, & Kato, 2003), *Dictyota menstrualis* (Albuquerque et al., 2004), *Kjellmaniella crassifolia* (Sakai, Kimura, & Kato, 2002), *Hizikia fusiforme* (Li, Wei, Sun, & Xu, 2006), *Analipus japonicus* (Bilan et al., 2007), and *Chorda filum* (Chizhov, Dell, & Morris, 1999). The low-molecular-weight fractions of algal fucoidans (less than 30 kDa) obtained by depolymerization have been shown to exhibit some heparin-like properties, with less side effects (Karim et al., 2011). Such polysaccharides do not occur in other divisions of algae and in land plants. However, the related biopolymers were found in marine invertebrates such as sea cucumbers (*Ludwigothurea grisea*) or sea urchins (*Lytechinus variegatus*, *Arbacia lixula*, *Strongylocentrotus purpuratus*, *S. franciscanus*, *S. pallidus*, and *S. droebachiensis*) (Alves, Mulloy, Diniz, & Mourao, 1997; Alves, Mulloy, Moy, Vacquier, & Mourao, 1998; Mulloy, Ribeiro, Alves, Vieira, & Mourao, 1994; Ribeiro, Vieira, Mourao, & Mulloy, 1994; Vilela-Silva, Alves, Valente, Vacquier, & Mourao, 1999; Vilela-Silva, Castro, Valente, Biermann, & Mourao, 2002). These polysaccharides are simpler than fucoidans derived from marine brown algae and are referred to as sulfated fucans (Karim et al., 2011).

2.2. Molecular structure

Since Kylin firstly isolated fucoidan in 1913, the structures of fucoidans from different brown seaweeds have been investigated. The seaweed fucoidans are heterogenic and represent the mixtures of structurally related polysaccharides with certain variations of the content of carbohydrate units and non-carbohydrate substituents (Cumashi et al., 2007). Fucoidans are mainly composed of fucose and sulfate. Besides, they also contain other monosaccharides (mannose, galactose, glucose, xylose, etc.) and uronic acids, even acetyl groups and protein (Bo et al., 2008). The fucoidans of most algae consist of

Table 1 – Various biological activities of seaweed fucoidans.

Sources	Activities	Effectiveness	Ref.
Ecklonia cava	Anti-coagulant	Inhibiting biological activity of serine proteases II, X, and VII	Athukorala et al. (2006)
Undaria pinnatifida	Anti-virus	Blocking HSV-1 and HSV-2 replication	Lee et al. (2004)
		Protecting mice from infection with HSV-1	Cooper et al. (2002)
Dictyota mertensii, *Lobophora variegate*, *Spatoglossum schroederi*, and *Fucus vesiculosus*		Inhibiting HIV reverse transcriptase	Queiroz et al. (2008)
Ecklonia cava	Anti-inflammation	Suppressing inflammatory response in LPS-stimulated RAW 264.7 cells	Kang et al. (2011)
Fucus vesiculosus		Suppressing inflammatory response in LPS-induced microglia cells	Park et al. (2011a)
Undaria pinnatifida	Anti-allergy	Augmenting Th1 cell response in normal BALB/c mice and inhibiting Th2 cell response	Maruyama et al. (2005)
		Reducing IgE level in mice serum	
Laminaria japonica	Antioxidant	Scavenging superoxide radical and hypochlorous acid	Zhao et al. (2005)
		Inhibiting low-density lipoprotein oxidation induced by Cu^{2+}	Li et al. (2002)
		Preventing the increase of lipid peroxide in serum, liver, and spleen of diabetic mice	
Focus vesiculosus	Anti-obesity	Inhibiting fat accumulation through the regulation of lipolysis in 3T3-L1 adipocytes	Park et al. (2011b)
Cladosiphon okamuranus	Anti-tumor	Inducing apoptosis via caspase-3 and -7 activation-dependent pathways	Teruya et al. (2007)
Cladosiphon okamuranus	Gastric protection	Inhibiting the growth of stomach cancer cells without any effects on normal cells	Shibata et al. (2000) Kawamoto et al. (2006)
Fucus vesiculosus	Against hyperoxaluria	Preventing the increased excretion of calcium oxalate monohydrate crystals	Veena et al. (2007a)

sulfated L-fucose with major fucose components (Kloareg, Demarty, & Mabeau, 1986). However, some fucoidans have minor fucose components and major other monosaccharides like galactose (Xue et al., 2001) or uronic acids (Mabeau, Kloareg, & Joseleau, 1990; Nishino, Nishioka, Ura, & Nagumo, 1994). According to Cumashi et al. (2007), the polysaccharide backbones in fucoidans are known as type I or type II chains (Fig. 1). The type I chains are found to contain the repeating (1 → 3)-linked α-L-fucopyranose residues, whereas type II chains contain the alternating (1 → 3)- and (1 → 4)-linked α-L-fucopyranose residues. Moreover, it is observed that the sulphation may occur at positions 2, 3, and 4 and the monosaccharides are associated via α-1,2, α-1,3, or α-1,4 glycosidic bonds (Holtkamp, Kelly, Ulber, & Lang, 2009).

2.3. *Physiological properties*

The role of most fucoidans in marine organisms is not investigated well. For algae, some studies have shown a correlation between fucoidan content and the depth at which they grow. The content of fucoidan is lots at inter-tidal zone and less at zone under the low water line. That difference was suggested to be due to the conservation against dehydration (Black, 1954; Black, Dewar, & Woodward, 1952). Moreover, fucoidans are as well supposed to enhance cell wall stability and involved in the morphogenesis of algae embryos (Bisgrove & Kropf, 2001; Mabeau et al., 1990). In addition, the role of fucoidans is also known to be involved in fertilization of sea-urchin and in maintenance of the body wall's integrity of sea cucumber (Berteau & Mulloy, 2003).

3. Biological activities of fucoidans

3.1. *Anti-coagulant activity*

Coagulation is a complex process related to the formation of clots to end bleeding at an injured site. It is an important part of hemostasis, the cessation of blood loss from a damaged vessel, wherein a damaged blood vessel wall is covered by a platelet and fibrin-containing clot to stop bleeding and begin repair of the damaged vessel. Disorders in blood coagulation can lead to an increased risk of bleeding (hemorrhage) or clotting (thrombosis) (David, Nigel, Michael, & Denise, 2009). These illnesses have increased over the last decades and no useful new substances have been discovered to remediate them. So far, heparin, a highly sulfated polysaccharide present in mammalian tissues, has been used as an anti-coagulant drug for more than 50 years (Lindahl, 2000). However, the clinical use of heparin has been known to cause several side effects such as excessive bleeding, thrombocytopenia, mild transaminase elevation, and hyperkalemia (Tolwani & Wille, 2009). Thus, it is necessary to find the alternative drugs for heparin with safely and efficiently anti-coagulant properties. Notably, marine algae-derived fucoidan have been determined to be effective

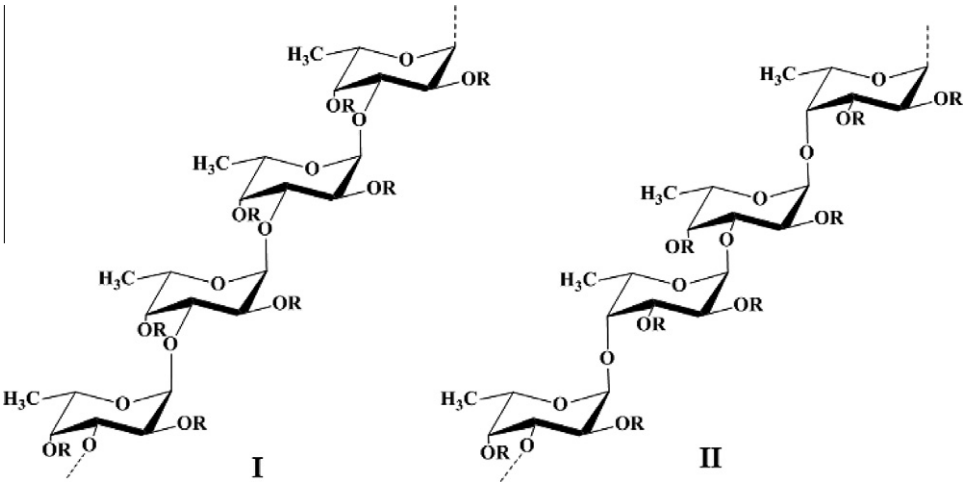

Fig. 1 – Type I and type II chains of brown seaweed fucoidans. R is potential attachment of carbohydrate (α-L-fucopyranose, α-D-glucuronic acid) and non-carbohydrate (sulfate and acetyl groups) substituents.

against blood coagulation. Many studies have proposed fucoidan as alternative agent to the anti-coagulant heparin (Mourao, 2004; Mourao & Pereira, 1999). So far, the anti-coagulant activity of fucoidan was reported by Springer, Wurzel, McNeal, Ansell, and Doughty (1957). It was shown that a certain fraction of fucoidan from *F. vesiculosus* possessed powerful anti-coagulant activity that qualified fucoidan to belong to the group of heparinoids. Moreover, Nishino and Nagumo (1987) has examined the anti-coagulant activities of fucoidans isolated from nine brown seaweed species, including activated partial thromboplastin time (APTT), thromboplastin time (TT), and anti-factor Xa activity in comparison with values of heparin (167 units/mg). It was found that fucoidan from *Ecklonia kurome* and *Hijikia fusiforme* exhibited the highest activity with respect to APTT (38 units/mg) and TT (35 units/mg) for E. *kurome* and APTT (25 units/mg) and TT (22 units/mg) for *H. fusiforme*. Presently, several different fucoidan preparations from various algal species, including *F. versiculosus* (Nishino et al., 1994), *Laminaria brasiliensis* (Mourao & Pereira, 1999), *E. kurome* (Nishino, Fukuda, Nagumo, Fujihara, & Kaji, 1999), *Ascophyllum nodosum* (Millet et al., 1999), *Pelvetia caniculata* (Colliec, Boisson-Vidal, & Jozefonvicz, 1994) have been reported for their anti-coagulant activity. Recently, anti-coagulant activities of fucose containing sulfated polysaccharide isolated from brown seaweed *E. cava* including APTT, TT, and PT have been reported by Athukorala and colleagues (Athukorala, Jung, Vasanthan, & Jeon, 2006). The anti-coagulant effect of this compound was observed to be similar with heparin. Further, fucose containing sulfated polysaccharide from *E. cava* has been shown to inhibit the activities of coagulation factors via interaction with antithrombin III in both the extrinsic and common coagulation pathways (Jung et al., 2007). The structures of fucoidan vary from their algal source species to species and must give rise to variation in the degree of most biological activities, including anti-coagulation action (Boisson-Vidal et al., 2000; Chevolot et al., 1999; Pereira, Mulloy, & Mourao, 1999). Many studies showed that the anti-coagulant activity of fucoidan have relation with sulfate group and carbohydrate content. In particular, Nishino and colleagues have revealed that the higher content of fucose and sulfate groups presents the higher anti-coagulant activity in native fucoidans from *E. kurome* (Nishino & Nagumo, 1991a, 1992; Nishino, Yokoyama, Dobashi, Fujihara, & Nagumo, 1989). Moreover, the position of sulfate groups on sugar residues is also very important for the anti-coagulant activity of fucoidan. It was identified that the concentrations of C-2 sulfate and C-2,3 disulfate of fucoidans have relationship with anti-coagulant activity (Chevolot, Mulloy, & Racqueline, 2001; Chevolot et al., 1999). Duarte et al. (2001) determined that the anti-coagulant effect of fucoidans was mainly related to the fucose sulfated chains, specially the disulfated fucosyl units. Silva et al. (2005) reported that 3-O-sulphation at C-3 of 4-α-L-fucose-1→ units was responsible for the anti-coagulant properties of fucoidan from *Padina gymnospora*. On the other hand, the correlation between molecular weight of fucoidans and their anti-coagulant activity have been found in recent studies even though it was not determined exactly. Particularly, the higher molecular weight fucoidans such as 27 and 58 kDa exhibited stronger anti-coagulant effect than lower molecular weight fucoidan (~10 kDa) (Nishino, Aizu, & Nagumo, 1991b). The native fucoidan (MW 320,000 Da) from *Lessonia vadosa* showed good anti-coagulant activity, whereas the radical depolymerized fraction (MW 32,000 Da) presented weak anti-coagulant activity (Chandía & Matsuhiro, 2008). Similarly, Pomin and colleagues also confirmed the relationship between molecular weight of fucoidan and their anti-coagulant activity. Selective cleavage to reduce molecular size of the fucoidan dramatically reduced its effect on thrombin inactivation mediated by heparin cofactor II (Pomin et al., 2005). Accordingly, fucoidans have been suggested to be potential biological materials in treatment of blood coagulant disorders.

3.2. *Anti-viral activity*

Sulfated polysaccharides have been known to be capable of inhibiting the replication of enveloped viruses including herpes simplex virus (HSV) and human immunodeficiency virus (HIV) (Jiao, Yu, Zhang, & Ewart, 2011). Their inhibition exhibit low cytotoxicity compared with other anti-viral drugs currently used in clinical medicine. Notably, fucoidans can effectively prevent the penetration of viruses to cells on account of the

modification of properties of cellular surface, although direct interaction of polysaccharides with viral surface proteins or viral enzymes is also possible (Usov & Bilan, 2009). The blockade of fucoidans on HSV infection has been reported in numerous recent studies. Feldman, Reynaldi, Stortz, Cerezo, and Damont (1999) isolated fucoidan fractions (Ee, Ec, and Ea) from *Leathesia difformis* and determined their selective anti-viral abilities against HSV-1 and HSV-2. Fucoidan Ea was shown to be the most active agent, with IC_{50} value in the range 0.5–1.9 μg/mL. Continually, fucoidans were found in different brown macroalgae due to their anti-HSV properties, including *Adenocystis utricularis*, *S. horneri*, *Cystoseira indica*, *Stoechospermum marginatum*, and *S. tenerrimum* (Adhikari et al., 2006; Mandal et al., 2007; Ponce, Pujol, Damonte, Flores, & Stortz, 2003; Preeprame, Hayashi, Lee, Sankawa, & Hayashi, 2001; Sinha, Astani, Ghosh, Schnitzler, & Ray, 2010). Noticeably, *Undaria pinnatifitida*, the most commonly eaten brown seaweed in Japan, contains sulfated polyanions and other components with appreciable anti-HSV effect. Galactofucan, the major component of an aqueous extract of *Undaria pinnatifida*, was evaluated for antiviral activity against 32 clinical strains of HSV, including 12 ACV-resistant strains (four HSV-1 and eight HSV-2) and 20 ACV-susceptible strains (10 HSV-1 and 10 HSV-2). The median IC_{50} of galactofucan for the 14 strains of HSV-1 and 18 strains of HSV-2 was 32 and 0.5 μg/mL, respectively. It was indicated that galactofucan is significantly more active against clinical strains of HSV-2 than HSV-1. The mode of action of the galactofucan was shown to be the inhibition of viral binding and entry into the host cell (Thompson & Dragar, 2004). In addition, a fucoidan from sporophyll of *U. pinnatifida* was examined for its anti-viral activity. The IC_{50} value for HSV-1 and HSV-2 were 2.5 and 2.6, respectively, under conditions in which the fucoidan was added at the same time as viral infection (Lee, Hayashi, Hashimoto, Nakano, & Hayashi, 2004). In the *in vivo* conditions, ingestion of fucoidan from *U. pinnatifida* was associated with increased healing rates in patients with active infections (Cooper et al., 2002). Moreover, oral administration of the fucoidan from *U. pinnatifida* could protect mice from infection with HSV-1 as judged from the survival rate and lesion scores (Hayashi, Nakano, Hashimoto, Kanekiyo, & Hayashi, 2008a). Substantially, natural killer and cytotoxic T lymphocytes activity in HSV-1-infected mice was enhanced by oral administration of the fucoidan. The production of neutralizing antibodies in the mice inoculated with HSV-1 was significantly promoted during the oral administration of the fucoidan for 3 weeks. According to these results, fucoidan from *U. pinnatifida* was suggested as a topical microbicide for the prevention of transmission of HSV through direct inhibition of viral replication and stimulation of both innate and adaptive immune defense functions. On the other hand, fucoidans have been found to exhibit anti-HIV activity with different mechanisms of action. According to Queiroz et al. (2008), the fucoidan from *Dictyota mertensii*, *Lobophora variegata*, *Spatoglossum schroederi*, and *Fucus vesiculosus* were reported to inhibit HIV reverse transcriptase (RT). They have indicated that the galactofucan fraction from *L. variegate*, which is rich in galactose, fucose, and glucose with a lower sulfate content, had a marked inhibitory effect on reverse transcriptase, with 94% inhibition for synthetic polynucleotides at a concentration of 1.0 μg/mL. Moreover, fucan A from *S. schroederi* and *D. mertensii*, which contains mainly fucose with a lower sulfate level, showed a high inhibitory effect on RT enzyme at 1.0 mg/mL, with 99.03% and 99.3% inhibition, respectively. Meanwhile, fucan B from *S. schroederi*, which contains galactose, fucose and high sulfate level, showed a lower inhibitory activity (53.9%) at the same concentration. Taking another approach, the authors purified a fucan fraction from *F. vesiculosus*, a homofucan containing only sulfated fucose with high sulfate content, which exhibited high inhibitory activity of HIV on RT. This fraction inhibited 98.1% of the reaction with poly(rA)-oligo(dT) at a concentration of 0.5 mg/mL (Queiroz et al., 2008). In the recent study, Trinchero et al. (2009) have shown that galactofucan fractions from the brown algae *Adenocystis utricularis* exhibited anti-HIV-1 activity *in vitro*. Among five fractions, EA1–20 and EC2–20 had a strong inhibitory effect on HIV-1 replication with low IC_{50} values (0.6 and 0.9 μg/mL, respectively). Additionally, EA1–20 and EC2–20 displayed this capacity against wild type and drug-resistant HIV-1 strains. For active fractions, it was also shown that the inhibitory effect was not due to an inactivating effect on the viral particles but rather to a blockade of early events of viral replication. Based on these results, seaweed-derived fucoidans are regarded as good candidates for further studies on prevention of HIV-1 infection.

3.3. *Anti-inflammatory activity*

Inflammation is a critically important aspect of host responses to various stimuli including physical damage, ultraviolet irradiation, microbial invasion, and immune reactions. It is associated with a large range of mediators that initiate the inflammatory response, recruit, and activate other cells to the site of inflammation. However, excessive or prolonged inflammation can prove harmful, contributing to the pathogenesis of a variety of diseases, including chronic asthma, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, psoriasis, and cancer (Vo, Ngo, & Kim, 2012). Meanwhile, fucoidans derived from marine algae have been demonstrated to inhibit inflammatory response in many recent studies. According to Kang et al. (2011), the inhibitory effect of sulfated polysaccharide containing fucose from *E. cava* on inflammatory response have been investigated in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells. It was found that this algal fucoidan dose-dependently inhibited nitric oxide (NO) and prostaglandin E_2 (PGE_2) production by suppressing the expression of NO synthase (iNOS) and cyclooxygenase (COX)-2 at the proten levels. Also, fucoidan were found to possess suppressive effect on neuroinflammatory response in LPS-induced microglia cells (Cui et al., 2010; Park et al., 2011a). Cui et al. (2010) showed that fucoidan from *Laminaria japonicaon* exhibited inhibitory effect on NO production and expression. In the next study, Park and collaborators have also reported that the treatment of fucoidan from *Fucus vesiculosus* significantly inhibited excessive production of NO and PGE_2 accompanied by suppressing the expression of iNOS and COX-2 (Park et al., 2011a). Moreover, fucoidan treatment caused decrease in production and expression of monocyte chemoattractant protein-1 (MCP-1) and pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumor necrosis factor (TNF)-α. Notably, fucoidan exhibited anti-inflammatory properties by suppression of nuclear factor-kappa B (NF-κB) activation and down-regulation of extracellular

signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), and AKT pathways (Cui et al., 2010; Park et al., 2011a). In an *in vivo* experiment, potential inhibitory mechanisms of fucoidan on rat myocardial ischemia–reperfusion (I/R) model have been evaluated by Li et al. (2011). The administration of fucoidan resulted in reduction of myocardial infarct size, serum levels of TNF-α and IL-6, and the activity of myeloperoxidase. Furthermore, fucoidan down-regulated the expression of high-mobility group box 1, phosphor-IκB-α, and NF-κB. Besides, the infiltration of polymorph nuclear leukocytes and histopathological damages in myocardium were decreased in fucoidan-treated groups. These findings revealed that the administration of fucoidan could regulate the inflammation response via high-mobility group box 1 and NF-κB inactivation in I/R-induced myocardial damage. In another sense, it was reported that connective tissue destruction during inflammatory diseases, such as chronic wound, chronic leg ulcers, or rheumatoid arthritis, is the result of continuous supply of inflammatory cells and exacerbated production of inflammatory cytokines and matrix proteinases (Senni et al., 2006). Herein, fucoidan from *Ascophyllum nodosum* is known to be a potent modulator of connective tissue proteolysis (Senni et al., 2006). Thus, fucoidan was suggested to be used for treating some inflammatory pathologies in which uncontrolled extracellular matrix degradation takes place. So far, the selectin family, which expressed on endothelial cells, leukocytes, and platelets, has been evidenced to contribute to the interactions of leukocytes and platelets at the side of vascular injury. Such interactions enhance inflammatory reactions during the arterial response to injury (Ley, 2003). Especially, the interaction of selectin with its ligand is effectively inhibited by fucoidans (Bachelet et al., 2009; Chauvet, Bienvenu, Théorêt, Latour, & Merhi, 1999; Preobrazhenskaya et al., 1997; Semenov et al., 1998), and and thus reducing inflammation process at its earlier stages.

3.4. *Anti-allergic activity*

Allergy is a disorder of the immune system due to an exaggerated reaction of the immune system to harmless environmental substances, such as animal dander, house dust mites, foods, pollen, insects, and chemical agents. The initial event responsible for the development of allergic diseases is the generation of allergen-specific CD^{4+} type 2 helper (Th2) cells. Once generated, effector Th2 cells produce IL-4, IL-5, IL-9, and IL-13 which cause the production of allergen-specific IgE by B cells. Subsequently, allergic reactions are induced upon binding of allergen to IgE, which is tethered to the high affinity IgE receptor on the surface of mast cells and basophils (Vo et al., 2012). Hence, IgE and Th2 cytokines are considered as the potential targets for anti-allergic therapeutics. Interestingly, algal fucoidans have been found to suppress IgE and Th2 cytokine production as shown in recent studies. According to Maruyama and co-workers, fucoidan obtained from *U. pinnatifida* is able to augment Th1 cell response in normal BALB/c mice, which contribute to the inhibition of Th2 cell response (Maruyama, Tamauchi, Hashimoto, & Nakano, 2005). Indeed, the production of Th2 cytokines including IL-4 and IL-13 in bronchoalveolar lavage fluid was suppressed when fucoidan was injected intraperitoneally. Moreover, anti-ovalbumin (OVA) immunoglobulin E (IgE) and IgE levels in serum determined after challenge with aerosolized OVA at the end of the experiment were reduced in the fucoidan-treated mice (Maruyama et al., 2005). Likewise, Yanase et al. (2009) determined that the OVA-induced increase of plasma IgE was significantly suppressed when fucoidan was intraperitoneall. Further, the production of IL-4 in response to OVA in spleen cells isolated from OVA-sensitized mice treated with fucoidan was lower than that from mice treated without fucoidan. Specially, the flow cytometric analysis and ELISpot assay revealed that the administration of fucoidan suppressed a number of IgE-expressing and IgE-secreting B cells, respectively. In an *in vitro* experiment, Oomizu, Yanase, Suzuki, Kameyoshi, and Hide (2006) have confirmed that fucoidan inhibited the production of IgE and Cε germline transcription in murine B cells induced by IL-4 and anti-CD40 antibodies. Yet, the inhibitory activity of fucoidan has been not observed if B cells were pre-stimulated with IL-4 and anti-CD40 antibody before the administration of fucoidan. Thus, it suggested that fucoidan may not prevent a further increase of IgE in patients who have already developed allergic diseases and high levels of serum IgE. However, Iwamoto et al. (2011) have recently determined that fucoidan effectively reduced IgE production in both peripheral blood mononuclear cells from atopic dermatitis patients and healthy donors. These findings indicated that fucoidan suppresses IgE production by inhibiting immunoglobulin class-switching to IgE in human B cells, even after the onset of atopic dermatitis.

3.5. *Antioxidant activity*

The oxidants such as superoxide anion, hydrogen peroxide, hydroxyl radicals, and singlet oxygen are well-known to cause various chronic diseases (Waris & Ahsan, 2006). Antioxidants may have a positive effect on human health as they can protect the human body against damage by reactive oxygen species (ROS), which attack macromolecules such as membrane lipids, proteins, and DNA, lead to many health disorders such as cancer, diabetes mellitus, neurodegenerative, and inflammatory diseases with severe tissue injuries (Ngo, Wijesekara, Vo, Ta, & Kim, 2011). Recently, there is a considerable interest in the food industry as well as pharmaceutical industry for the development of antioxidants from natural sources as safe alternatives of many synthetic commercial antioxidants. Among them, fucoidans derived from marine algae have been found as great antioxidants via their scavenging effect on biologically harmful oxidants. Fucoidan from the edible seaweed *F. vesiculosus* was shown to prevent the formation of superoxide radicals (IC_{50} 58 μg/mL), hydroxyl radicals (IC_{50} 157 μg/mL), and lipid peroxidation (IC_{50} 1250 μg/mL) (Micheline et al., 2007). Moreover, fucoidan fractions F-A and F-B from *L. japonica* exhibit excellent scavenging capacities on superoxide radical and hypochlorous acid, except the highly sulfated fraction L-B. Especially, low molecular weight fractions L-A and L-B possess great inhibitory effects on low-density lipoprotein (LDL) oxidation induced by Cu^{2+} (Zhao, Xue, Cai, Wang, & Fang, 2005). The superoxide radical scavenging ability of fucoidan obtained from *L. japonica* has been also confirmed by Wang and colleagues (Wang, Zhang, Zhang, & Li, 2008). In the same regard, Zhao, Wang, and Xue (2011) have determined

that fucoidan F-C from *L. japonica* with low molecular weight 2000–8000 and sulfate content 24.3% had much strong protective effect on both hydrophilic radical AAPH and lipophilic radical AMVN-induced LDL oxidation. Further, the highly sulfated fucoidan fraction L-B with molecular weight 20,000 Da was effectively suppressed the oxidant of LDL induced by AMVN. In an *in vivo* experiment, fucoidan from *L. japonica* was observed to be able to prevent the increase of lipid peroxide in serum, liver, and spleen of diabetic mice obviously (Li et al., 2002). Collectively, these results clearly indicate the beneficial effect of algal fucoidans as antioxidants which has great potential for preventing the free radical-mediated diseases.

3.6. *Anti-obesity activity*

Obesity is a chronic metabolic disorder caused by an imbalance between energy intake and expenditure. Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis (Kopelman, 2000; Spiegelman & Flier, 2001). In general, obesity is associated with the extent of adipocyte differentiation, intracellular lipid accumulation, and lipolysis (Park, Jung, & Roh, 2011b). Recently, there has been increasing interest in potential biological activity against obesity of fucoidan. Herein, Kim, Chang, and Lee (2009) evaluated protective effect of fucoidan from brown algae in 3T3-L1 adipocyte differentiation. They have suggested that fucoidan could be used for inhibiting fat accumulation, which is mediated by suppressing gene expression of fatty acid binding proteins, acetyl CoA carboxylase, and peroxisome proliferation-activated receptor γ. Moreover, Park et al. (2011b) has clearly investigated the inhibitory effects of fucoidan from *Focus vesiculosus* on lipid accumulation through the regulation of lipolysis in 3T3-L1 adipocytes. It was observed that the expressed protein levels of total hormone sensitive lipase (HSL) and its activated form, phosphorylated-HSL were significantly increased at concentration of 200 μg/mL fucoidan. Further, insulin-induced 2-deoxy-D-[3H] glucose uptake was decreased up to 51% in fucoidan-treated cells as compared to control. Evidently, the increase of HSL and p-HSL expression and decrease of glucose uptake into adipocytes lead to stimulation of lipolysis, and thus contributing to the reduction of lipid accumulation.

3.7. *Anti-tumor activity*

Since fucoidans do not exert cytotoxic activity, their anti-tumor is mainly accounted for by inhibiting the proliferation of tumor cells, stimulating the apoptosis of tumor cells, blocking tumor cell metastasis, and enhancing various immune responses. Indeed, the anti-proliferative activity of oversulfated fucoidan from commercially cultured *Cladosiphon okamuranus* TOKIDA in U937 cells has been observed (Teruya, Konishi, Uechi, Tamaki, & Tako, 2007). The inhibition of cell proliferation was caused by induction of apoptosis via caspase-3 and -7 activation-dependent pathways. Moreover, fucoidan from the brown seaweed *C. okamuranus* significantly inhibited the growth of peripheral blood mononuclear cells of adult T-cell leukemia patients and human T-cell leukemia virus (HTLV) type 1-infected T-cell lines but not that of normal peripheral blood mononuclear cells. Fucoidan induced apoptosis of HTLV-1-infected T-cell lines mediated through downregulation of cellular inhibitor of apoptosis protein-2 and surviving. *In vivo* use of this fucoidan resulted in partial inhibition of growth of tumors of an HTLV-1-infected T-cell line transplanted subcutaneously in severe combined immune deficient mice (Haneji et al., 2005). Additionally, fucoidan activates a caspase-independent apoptotic pathway in MCF-7 cancer cells through activation of ROS-mediated MAP kinases and regulation of the Bcl-2 family protein-mediated mitochondrial pathway (Zhang, Teruya, Eto, & Shirahata, 2011). Likewise, the Miyeokgui fucoidan showed anti-tumor activity against PC-3 (prostate cancer), HeLa (cervical cancer), A549 (alveolar carcinoma), and HepG2 (hepatocellular carcinoma) cells, in a similar pattern to that of commercial fucoidan (Synytsya et al., 2010). Also, fucoidan from *F. vesiculosus* induces apoptosis of human HS-Sultan cells accompanied by activation of caspase-3 and down-regulation of ERK pathways (Aisa et al., 2005). Fucoidans from *L. saccharina*, *L. digitata*, *F. serratus*, *F. distichus*, and *F. vesiculosus* strongly blocked MDA-MB-231 breast carcinoma cell adhesion to platelets, which might have critical implications in tumor metastasis (Cumashi et al., 2007). According to Liu et al. (2005), fucoidan inhibits the adhesion of MDA-MB-231 cells to fibronectin by blocking the protein's heparin- and cell-binding domains, modulating the reorganization of the integrin alpha5 subunit, down-regulating the expression of vinculin. On the other hand, the anti-tumor activity of fucoidans was also found due to anti-metastatic activity. The administration (10 mg/kg) of fucoidan from seaweed *F. evanescens* in C57Bl/6 mice with transplanted Lewis lung adenocarcinoma produced the inhibitory effect against metastasis and potentiated the anti-metastatic, but not anti-tumor effects of cyclophosphamide (Alekseyenko et al., 2007). Further, Coombe, Parish, Ramshaw, and Snowden (1987) have reported that lung metastases resulting from the intravenous injection of cells from the rat mammary adenocarcinoma 13762 MAT were significantly reduced by a variety of sulfated polysaccharides such as fucoidan and heparin.

Another mechanism of the anti-tumor activity of fucoidans is known due to the anti-angiogenic effect since fucoidans suppress the intensive formation of vessels and so reduce the active supply of blood to tumor tissues (Koyanagi, Tanigawa, Nakagawa, Soeda, & Shimeno, 2003; Soeda, Shibata, & Shimeno, 1997). Besides, fucoidans inhibit tumor growth and metastatic process by the enhancement of immune responses. Fucoidan increases the quantity of macrophages (Song, Xu, & Zhang, 2000), and mediates tumor destruction through type 1 T-helper (Th1) cell and NK cell responses (Maruyama, Tamauchib, Iizuka, & Nakano, 2006). Fucoidan activates lymphocytes and macrophages mediated by production of free radicals (NO and H_2O_2) and cytokines (TNF-α and IL-6), and thus contributing to their effectiveness in the immunoprevention of tumor (Choi, Kim, Kim, & Hwang, 2005). Overall, finding of anti-tumor properties of brown algal fucoidans could elevate the value of brown seaweeds as functional ingredients in functional foods or pharmaceuticals.

3.8. *Other biological activities of fucoidan*

Fucoidan derived from *C. okamuranus* tokida has been known to be safe compound for gastric protection (Shibata et al., 2000). It

was shown to inhibit the growth of stomach cancer cells but did not show any effects on normal cells (Kawamoto et al., 2006). Fucoidan prevented concanavalin A-induced liver injury by mediating the endogenous interleukin (IL)-10 production and the inhibition of proinflammatory cytokine in mice (Saito et al., 2006). Moreover, hepatic fibrosis induced by CCl_4 was also attenuated by injection of fucoidan (Hayashi et al., 2008b). On the other hand, fucoidan administration was able to maintain the integrity of erythrocyte membrane and decrease the damage to erythrocytes in hyperoxaluria (Veena, Josephine, Preetha, & Varalakshmi, 2007a). Fucoidan treatment can prevent the increased excretion of calcium oxalate monohydrate crystals in urine along with crystal deposition in renal tissues (Veena, Josephine, Preetha, & Varalakshmi, 2007b). The oral intubation of fucoidan significantly reduced the elevated urinary protein excretion and plasma creatinine due to the induction of Heymann nephritis. This indicated that fucoidan has a renoprotective effect on active Heymann nephritis and is a promising therapeutic agent for nephritis (Zhang et al., 2005).

4. Conclusion

The increasing health consciousness has been one of the most important stimulating factors for rapid global growth of the functional food industry. Herein, marine sources have received much attention since a large number of phytochemicals and bioactives present in marine organisms. Notably, fucoidans have been evidenced to play a vital role in human health and nutrition due to their numerous biological activities and health benefit effects. Thus, the extensive studies of fucoidans will discover novel biological properties as well as novel functional applications in pharmaceuticals, nutraceuticals, cosmeceuticals, and functional foods.

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