CHAPTER 4

Potential Role of Marine Algae on Female Health, Beauty, and Longevity

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Contents

Abstract

Marine environment has been known as a rich source of chemical structures with numerous health benefit effects. Among marine organisms, marine algae have been identified as an underexploited plant resource although they have long been recognized as valuable sources of structurally diverse bioactive compounds. Presently, several lines of studies have provided insight into biological activities of marine algae in promoting female health, beauty, and longevity. Hence, marine algae have a great potential to be used as

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a part of pharmaceuticals, nutraceuticals, and functional foods. This contribution presents an overview of marine algal potential effect in promoting female health, beauty, and longevity.

I. INTRODUCTION

More than 70% of the Earth's surface is covered by oceans with marine species comprising approximately half of the total global biodiversity (Kim and Wijesekara, 2010; Swing, 2003). Hence, marine organisms are being recognized as rich sources of functional materials which are elicited by marine organisms to help them survive in the hostile ocean environment (Shahidi, 2008; Shahidi and Janak Kamil, 2001). Among marine organisms, marine algae are still identified as an underexploited plant resources; although they have been used as food sources since ancient times (Heo *et al*., 2009b; Pangestuti and Kim, 2011).

In Asian culture, marine algae have always been of particular interest as marine food sources (Khan *et al*., 2010). Edible marine algae or sometimes referred as seaweeds or sea vegetables accounted for more than 10% of Japanese diet with average consumption reaching an average of 1.4 kg/person/year (Burtin, 2003). In Korea, 37 days after delivering their babies, new mothers served with *miyeok-guk* which is a hot and spicy marine algae soup (Dennis *et al*., 2007). Korean believes that *miyeok-guk* provide nutrition and help the new mother to regain their energy. Marine algae have been demonstrated as rich sources of structurally diverse biologically active compounds with great pharmaceutical and biomedical potential; therefore, it represents one of the most nutritious plant foods. Several epidemiologic studies provided evidence that marine algae consumption correlates with low breast cancer rates in East Asia. As an example, 1 year prevalence case of breast cancer rates per 100,000 populations in Japan and China are 42.2 and 13.1, respectively, versus 125.9 and 106.2 cases in North America and Europe, respectively (Pisani *et al*., 2002; Yuan and Walsh, 2006).

In recent years, biological activities, nutritional value, and potential health benefits of marine algae have been intensively investigated and reviewed. In spite of extensive studies and reviews on nutritional value and potential health benefits of marine algae for human, there is little available literature that focuses on potential benefits of marine algae for female subject. Therefore, this chapter focuses on biological roles of marine algae and presents an overview of their potential benefits for female health and beauty.

II. POTENTIAL ROLE OF MARINE ALGAE ON FEMALE HEALTH, BEAUTY, AND LONGEVITY

A. Anticancer activity

Breast cancer is the leading cause of cancer-related death among females worldwide (Geyer *et al.*, 2006; Parkin, 2001). Globally, more than 1.1 million females are diagnosed each year, representing around 10% of all newly diagnosed cancer cases (Anderson *et al.*, 2006). The mortality rate for premenopausal breast cancer is almost four times greater in the Western world, compared with East Asia nation. In breast cancer etiology, genetics are thought to play a smaller role compared to environmental factors such as food diets. One important difference in the diet of East Asian populations compared to Western populations is higher amount of fish and marine algae consumption. As mentioned earlier, ancient tradition of marine algae consumption has made a large number of epidemiological researches showing the health benefit in females linked to marine algae consumption.

Three decades ago, Teas *et al.* investigated effect of *Laminaria angustata* consumption and development of breast cancer in female Sprague-Dawley rats induced with the carcinogen 7,12-dimethylbenz(a)anthracene (DMBA), a widely used rat mammary cancer model (Huggins *et al.*, 1961; Teas *et al.*, 1984). Diet containing 5% *L. angustata* was found to be effective in delaying the time of DMBA-induced tumor developments. Although the mechanism for *L. angustata* activity is not elucidated yet, the authors argue that bioactivity of *L. angustata* might bring by their nutrient content such as polyphenols, sulfated polysaccharides, vitamins, minerals, carotenoids, etc. In accordance, *wakame* (*Undaria pinnatifida*) and *mekabu* (sporophyll of wakame) have been demonstrated to reduce the incidence, multiplicity, and size of breast tumors in female Sprague-Dawley rats induced with DMBA (Funahashi *et al.*, 1999, 2001). Considering that *wakame* and *mekabu* are particularly rich in iodine, the investigators suggested that the cancer inhibition was brought about by the iodine. More recently, statistical correlations between dietary intake of iodine and breast cancers have been carried out; however, their exact mechanisms of action are not yet completely understood (Ellerker, 1955; Majem *et al.*, 1988).

Apoptosis or programmed cell death is a key process in cancer development and progression which can be characterized through distinct set of morphological and biochemical progresses. Inactivation of apoptosis has been considered to be one of the six fundamental hallmarks of cancer; therefore, apoptosis is a major target of cancer therapy development up to present (Brown and Attardi, 2005). Dioxinodehydroeckol, a phloroglucinol derivative from *Ecklonia cava,* has a potential inhibitory effect against growth of human breast cancer cells MCF-7 via induction of apoptosis

(Kong *et al*., 2009). Further, 1 μg/ml mekabu strongly induced apoptosis in three human breast cancer cell line (MCF-7, T-47D, and MDA-MB-231), the induction of apoptosis even greater than 5-fluorouracil, a chemotherapeutic agent frequently used in human breast cancer clinics. Hence, developing of novel molecules derived from marine algae which promote apoptosis in breast cancer cells by targeting both the intrinsic and extrinsic apoptotic pathways may lead to the development of effective breast cancer therapies.

Estrogen-dependent cancers such as breast, endometrial, and ovarian cancer are among the leading causes of morbidity and mortality in American females (Kramer and Wells, 1996). Increased incidence of these cancers is predicted in the future, and the need for primary prevention is clear. Epidemiological studies demonstrated that incidence rates of estrogen-dependent cancers are among the highest in Western, industrialized countries, while rates are much lower in China and Japan (Parkin *et al*., 1999, 2002). Due to some research study, low estrogen-dependent cancer rates have been attributed to the soy-rich and marine algae diets inherent among Asian populations (Teas *et al*., 2009). As an example, dietary intake of *Alaria esculenta* and soy protein has been reported to modify estrogen and phytoestrogen metabolism in healthy postmenopausal females (Teas *et al*., 2009). In another female pilot study, Skibola (2004) demonstrated that intake of *Fucus vesiculosus* (bladderwrack) significantly increased the total number of days of the menstrual cycle, reduced circulating 17β-estradiol levels, and elevated serum progesterone levels in premenopausal women with abnormal menstrual cycling histories (Skibola, 2004). Moreover, *F. vesiculosus* have been demonstrated to modulate endocrine hormones in female Sprague-Dawley rats and human luteinized granulose cells (Skibola *et al*., 2005). Hence, it may assumed that intake of marine algae may contribute to the lower estrogen circulating level which may correlate to the lower incidence of hormone-dependent cancers in females.

Cervical cancer is the second most common cancer in females worldwide and more females die annually because of cervical cancer rather than from AIDS (ElHage, 2005; Kaplan-Myrth and Dollin, 2007; Munoz *et al*., 2003). It is the principal cancer of female in most developing countries, where 80% cases occur (Munoz *et al*., 2003). Recent reports demonstrated that several marine algae species: *Palmaria palmate* (dulse), *Laminaria setchellii*, *Macrocystis integrifolia*, *Nereocystis leutkeana*, *Udotea flabellum*, and *Udotea conglutinate* extracts were able to inhibit cervical cancer cell proliferations *in vitro* (Moo-Puc *et al*., 2009; Yuan and Walsh, 2006; Yuan *et al*., 2005). The goal of most current cancer therapy is to reduce the number of tumor cells and to prevent their further accumulation. Hence, antiproliferative activity of marine algae in cervical cancer cells demonstrated potential of marine algae as therapeutic agent for cervical cancer treatment.

In addition, formation of cancer cells in human body can be directly induced by free radicals and natural anticancer drugs as chemopreventive agents have gained a positive popularity in treatment of cancer. Therefore, marine algal radical scavenging compounds such as phlorotannins, sulfated polysaccharides, carotenoids, carbamol derivatives can be used indirectly to reduce cancer formation in the female body.

Taken together, marine algae and their secondary metabolites have shown promising anticancer activities, and hence, marine algae have a great potential to improve female health and longevity by being a part of anticancer medicinal foods and nutraceuticals. However, future studies are needed focusing on the synergistic benefits of consuming different marine algae species, recommended doses, and timing of intake and preparation methods for marine algae in order to maximize the desired effect in the prevention of cancer, particularly cancer which occurs mainly in female subject.

B. Antiviral activity

Infection by certain human papilloma virus (HPV) types in female genital has been associated with cervical cancer, hence HPV prevention has received great attention from scientific studies (Lehtinen and Dillner, 2002). The first generation of HPV vaccine is currently available on the market to prevent HPV infection (Paczos *et al.*, 2010). However, high cost of vaccine has been a cause for concern and will be too expensive for use in the developing world. Therefore, the search for potential anti-HPV candidates containing higher inhibitory activity and fewer prices has rise great interest in pharmaceutical industries. In this regard, natural bioactive compounds and their derivatives are potential source for the development of functional foods as new generation anti-HPV therapeutics which is more effective, less side effects, and less expensive.

A large number of marine algae contain significant quantities of complex structural sulfated polysaccharides which have been demonstrated as potent inhibitors of wide variety of viruses, such as HPV (Campo *et al.*, 2009; Pujol *et al.*, 2007; Witvrouw and De Clercq, 1997). Carrageenan, a sulfated polysaccharides of D-galactose and 3,6-anhydro-D-galactose extracted from the Rhodophyceae, has been used in food products for centuries. Recently, carrageenan has been shown to bear anti-HPV activity *in vitro* (Campo *et al.*, 2009). Buck *et al.* noted that carrageenan, particularly ι-carrageenan, inhibits HPV three orders magnitude more potent than heparin, a highly effective model for HPV inhibitor (Buck *et al.*, 2006). Carrageenan acts primarily by preventing the binding of HPV virions to cells and blocks HPV infection through a second, postattachment heparin sulfate-independent effect. Those mechanism is consistent by the fact that carrageenan resembles heparin sulfate, which is known as HPV-cell

attachment factor. Further, some of milk-based products which contain carrageenan block HPV infectivity *in vitro*, even when diluted million-fold (Buck *et al*., 2006). In another study, carrageenan has been reported to inhibit genital transmission of HPV in female mouse model of cervicovaginal (Roberts *et al*., 2007; Schiller and Davies, 2004). In addition, carrageenan was able to generate antigen-specific immune responses and antitumor effects in female (C57BL/6) mice vaccinated with HPV-16 E7 peptide vaccine (Zhang *et al*., 2010).

Based on these findings, carrageenan can be an alternative source of novel therapeutic candidate for HPV by being a part of food additives. There are numerous advantages of carrageenan over other classes of antiviral agents, such as relatively low production costs, broad spectrum of antiviral properties, low cytotoxicity, safety, wide acceptability, and novel modes of action, suggesting that carrageenan are promising candidates in the near future. However, further studies with clinical trials are needed for their anti-HPV activity in female subject.

C. Antiobesity activity

Obesity may occur in any gender, however, it is more likely to occur in females (Popkin and Doak, 1998; Rennie and Jebb, 2005). Obesity among females (from teens and seniors) continues to increase in many industrialized and developing countries, which cause a worrying health trend (Kelishadi, 2007). A detrimental effect of obesity on female reproductive system has been demonstrated consistently (Pettigrew and Hamilton-Fairley, 1997). Further, it is reported that media and sociocultural influence continue to pressure young female to be thin which promotes body dissatisfaction, eating disturbance, depression, and negative effect in young female (Stice *et al*., 2003). Therefore, female may pay a higher health price for obesity than male. Accordingly, many categories of natural and synthetic compounds which demonstrated as antiobesity drugs have been used by female to reduce their weight. However, synthetic antiobesity agents are believed to have certain side effects such as unacceptable tachycardia, hypertension, improve lipid blood levels, improve glucose metabolism, disturbance of female reproductive system, etc. (Bays, 2004). Hence, more scientific efforts have been dedicated to study medicinal foods that can act as antiobesity agents.

In the past four decades, researchers have found that soluble dietary fibers are negatively associated with obesity. Marine algae is particularly rich in two different types of fiber, soluble and insoluble (Table 4.1; Lahaye, 1991). *Eisenia bicyclis*, sometimes referred as Arame, contained more than 50% soluble fiber of its dry weight; the other brown algae species, *F. vesiculosus,* contained around 40% insoluble fiber per dry weight (Lahaye, 1991; Ruperez and Saura-Calixto, 2001). In human

TABLE 4.1 Soluble, insoluble, and total fiber (% dry weight) in some edible marine algae

Marine algae	Soluble fiber	Insoluble fiber	Total fiber	References
Chlorophyceae				
Ulva lactuca (Sea lettuces)	21.3	16.8	38.1	Burtin (2003)
Enteromorpha sp. (Ao nori)	17.2	16.2	33.4	Burtin (2003)
Rhodophyceae				
Porphyra teneri (Nori)	14.56	19.22	33.78	Ruperez and Saura-Calixto (2001)
Chondrus crispus (Irish moss)	22.25	12.04	34.29	Ruperez and Saura-Calixto (2001)
Phaeophyceae				
Hijiki fusiformis (Hijiki)	16.3	32.9	49.2	Lahaye (1991)
Himanthalia elongate (Sea spaghetti)	25.7	7.0	32.7	Lahaye (1991)
Eisenia bicyclis (Arame)	59.7	14.9	74.6	Lahaye (1991)
Undaria pinnatifida (Wakame)	17.31	16.26	33.58	Ruperez and Saura-Calixto (2001)
Laminaria digitata (Kombu)	9.15	26.98	36.12	Ruperez and Saura-Calixto (2001)
Fucus vesiculosus (Bladderwrack)	9.80	40.29	50.09	Ruperez and Saura-Calixto (2001)
Durvillaea antarctica	27.7	43.7	71.4	Ortiz *et al*. (2006)

body, soluble and insoluble fiber acts in a very different way. Consumption of marine algae soluble fiber such as carrageenan, agar, alginate are primarily associated with hypocholesterolemic and hypoglycemic effects (Panlasigui *et al*., 2003). In example, alginates have been shown to modulate appetite and energy intake in models of acute feeding. Upon reaction with gastric acid (acid-soluble calcium source), alginates undergo ionic gelation to form an alginate gel that can slow gastric emptying, stimulate gastric stretch receptors, reduce intestinal nutrient uptake, and influence the glycaemic response (Dettmar *et al*., 2011). In accordance, ingesting calcium-gelled, alginate-pectin twice per day has been reported to reduce spontaneous food intake in overweight and obese females (Pelkman *et al*., 2007). Further, insoluble fiber such as cellulose, xylans, mannans are associated with excretion of bile acids, increase fecal bulk, and decrease intestinal transit time (Burtin, 2003; Moore *et al*., 1998).

More recently, Maeda *et al.* reported that dietary intake of fucoxanthin significantly attenuates the weight gain of white adipose tissue (WAT) and expressed Uncoupling Protein 1 (UCP1) in diabetic/obese KKA^y female mice (Maeda *et al*., 2005, 2007). The potential involvement of fucoxanthin in attenuating the weight gain of WAT may correlate to the presence of unusual double allenic bonds at C-7′ position (Miyashita and Hosokawa, 2009). WAT is the predominant type of adipose tissue and commonly called ''fat'' in mammals (Trayhurn and Wood, 2005). Besides its role in energy storage, WAT is now recognized as an endocrine and active secretory organ through its production of biologically active mediators termed adipokines (Curat *et al*., 2006). Excess production of adipokines including proinflammatory factors and chemokines has been linked with obesity and plays an important role in the development of obesity-related disease (Trayhurn and Wood, 2005). Therefore, fucoxanthin activity to attenuate the weight gain of WAT in female mice demonstrated potential of fucoxanthin for the prevention and treatment of obesity and diabetes particularly in female subject. Dioxinodehydroeckol and 1-(3′,5′-dihydroxyphenoxy)-7-(2″,4″,6-trihydroxyphenoxy)-2,4,9-trihydroxydibenzo-1,4-dioxin, two phloroglucinol derivatives isolated from *E. cava*, have significantly inhibits adipocyte differentiation in 3T3-L1 cells suggesting its potential use as a functional ingredient in obesity management.

According to those findings, marine algae may serve as a potential candidate for functional foodstuffs with health benefits, especially for obesity management. Hence, negative effect in female subjects, particularly in young females, caused by pressures to be thin can be minimized by the application of marine algae in foods, pharmaceuticals, etc. Additionally, marine algae would develop a new approach for the treatment of obesity in addition to currently available antiobesity agents. Therefore,

marine algae would be a potent natural source for the development of foods and pharmaceuticals for the management of obesity.

D. Antiosteoporosis activity

Osteoporosis is a skeletal condition characterized by decreased bone mineral density (BMD) (mass/volume unit) that leads to an increased risk of fractures (Beikler and Flemmig, 2003). A number of studies have identified that osteoporosis occurs much more frequently in females compared to males (Cadarette *et al*., 2000; Hannan *et al*., 2000; Schuit *et al*., 2004). There are a number of reasons for the high prevalence of osteoporosis in females. First, at skeletal maturity, males have 30–50% bone mass compared to females (Christiansen, 1993; Nieves *et al*., 2005). Second, although decreased BMD occurs in both males and females with age, the decreased of BMD is substantially greater in females after menopause (Kanis *et al*., 1997; Riggs *et al*., 2004, 2008). Therefore, it is very important to help postmenopausal females to prevent them from progressing to osteoporosis.

Fujita *et al*. (1996) indicated that active absorbable algal calcium (AAA Ca) was effective for improving BMD in elderly subject. AAA Ca is a mixture of active absorbable calcium (AA Ca) and heated algal ingredients prepared by heating cleaned oyster and marine algae (*Cystophyllum fusiforme*) submaximally under reduced pressure (Fujita *et al*., 1996). Further, mineral-rich extract from red marine algae *Lithothamnion calcareum* has been demonstrated to increased mineral content and bone strength in female mice on a western-style diet (Aslam *et al*., 2010). However, it is not clear yet by which minerals on the algal extracts act to preserve bone structure and function in female mice. The algal extract is currently available as a food supplement under the name Aquamin (GRAS 000028) which currently used in various products for human consumption in Europe, Asia, Australia, and North America.

In addition, Das *et al*. demonstrated the effects of fucoxanthin on osteoclastogenesis. Treatment with 2.5 M fucoxanthin also induced apoptosis accompanied by activation of caspase-3 in osteoclast-like cells. Those *in vitro* studies suggest that fucoxanthin suppresses osteoclastogenesis via the inhibition of osteoclast differentiation and the induction of apoptosis in osteoclasts (Das *et al*., 2010). Hence, dietary fucoxanthin may be useful for the prevention of bone diseases such as osteoporosis and rheumatoid arthritis, which are known to be related to bone resorption.

Collectively, it may assume that marine algae would be a potent natural source for the development of functional foods and pharmaceuticals to prevent osteoporosis. Moreover, it is important to evaluate other marine algae species which may have a great potential as antiosteoporosis agent.

E. Skin whitening activity

Skin whitening has been in practice around the world with Asia as the largest market. As much Asian female preferred more fair skin tone, skin whitening product has become and continues to be the best selling skin care products in Asia (Wang *et al*., 1997). Tyrosinase inhibition is the most common approach to achieve skin hypo-pigmentation as this enzyme catalyzes the rate-limiting step of pigmentation. Despite the large number of tyrosinase inhibitors *in vitro*, only a few are able to show induced effects in clinical trials. In this chapter, we review some potential marine organisms with its effects on pigmentation of skin focusing mainly on tyrosinase inhibitors. Hence, development of novel tyrosinase inhibitors from natural resources continues to arouse great attention, and in recent years, marine algae have attracted great attention in the search of natural tyrosinase inhibitor agents (Solano *et al*., 2006).

Recently, Cha *et al*. investigated 43 indigenous marine algae for tyrosinase inhibiting activity (Cha *et al*., 2010). They reported that extracts from *Ecklonia cava* and *Sargassum silquastrum* exhibited excellent inhibitory effects on the pigmentation of zebra fish, which is due to their potential tyrosinase inhibitory activity. Fucoxanthin isolated from *Laminaria japonica* has been reported to suppress tyrosinase activity in UVB-irradiated guinea pig and melanogenesis in UVB-irradiated mice. Oral treatment of fucoxanthin significantly suppressed skin mRNA expression related to melanogenesis, suggesting that fucoxanthin negatively regulated melanogenesis factor at transcriptional level (Shimoda *et al*., 2010). Fucoxanthin and astaxanthin have been demonstrated to possess photoprotective properties in human fibroblast cells via inhibition of DNA damage and enhance antioxidant activity (Heo and Jeon, 2009). Further, potential whitening effects of diphlorethohydroxycarmalol isolated from *Ishige okamurae* have been reported (Heo *et al*., 2009a, 2010). Phloroglucinol derivatives, a common secondary metabolite constituents of brown algae, possess tyrosinase inhibitory activity due to its ability to chelate copper in this enzyme (Kang *et al*., 2004). Some phlorotannins such as 7-phloroeckol and dioxinodehydroeckol have been described to inhibit tyrosinase activity stronger than arbutin and kojic acids (Yoon *et al*., 2009). Flavonoid glycoside derived from *Hizikia fusiformis* has been reported as potential tyrosinase inhibitor. *H. fusiformis* is one of the most common edible brown macroalgae belonging to the Sargassaceae family (Ranathunga *et al*., 2006).

These evidences suggest that bioactive compounds derived from marine algae have a promising potential to be used as skin whitening agents. There are numerous advantages of marine algae, such as relatively low production costs, broad spectrum of skin whitening properties, low cytotoxicity, safety, wide acceptability, and novel modes of action,

suggesting marine algae as nutritious food which can be used to restore female beauty; however, further studies are needed with clinical trials for their whitening effects.

III. CONCLUSIONS

The wide range of biological activities associated with natural compounds derived from marine algae such as phlorotannins, alginates, sulfated polysaccharides, and carotenoids have potential to expand its nutritional and health beneficial values of marine algae in food industries. Further, the wide diversity of marine algae and numerous undiscovered unique metabolites present in marine algae are interesting sources to increase numbers of novel functional foods, which is beneficial for female health, beauty, and longevity. Accordingly, possibilities of designing new medicinal foods or nutraceuticals and pharmaceuticals derived from marine algae are promising. However, clinical trials are needed to confirm anticancer, antiviral, antiosteoporosis, and antiobesity activity of marine algae. In addition, further research studies are needed in order to investigate marine algae activities in female subjects.

REFERENCES

Anderson, B. O., Shyyan, R., Eniu, A., Smith, R. A., Yip, C. H., Bese, N. S., Chow, L. W. C., Masood, S., Ramsey, S. D., and Carlson, R. W. (2006). Breast cancer in limited-resource countries: An overview of the Breast Health Global Initiative 2005 guidelines. *Breast J.* **12**, S3–S15.

Aslam, M., Kreider, J., Paruchuri, T., Bhagavathula, N., DaSilva, M., Zernicke, R., Goldstein, S., and Varani, J. (2010). A mineral-rich extract from the red marine algae lithothamnion calcareum preserves bone structure and function in female mice on a western-style diet. *Calcif. Tissue Int.* **86**, 313–324.

Bays, H. (2004). Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes. Res.* **12**, 1197–1211.

Beikler, T. and Flemmig, T. (2003). Implants in the medically compromised patient. *Crit. Rev. Oral Biol. Med.* **14**, 305.

Brown, J. M. and Attardi, L. D. (2005). The role of apoptosis in cancer development and treatment response. *Nat. Rev. Cancer* **5**, 231–237.

Buck, C. B., Thompson, C. D., Roberts, J. N., Muller, M., Lowy, D. R., and Schiller, J. T. (2006). Carrageenan is a potent inhibitor of papillomavirus infection. *PLoS Pathog.* **2**, e69.

Burtin, P. (2003). Nutritional value of seaweeds. *Electron. J. Environ. Agric. Food Chem.* **2**, 6.

Cadarette, S., Jaglal, S., Kreiger, N., McIsaac, W., Darlington, G., and Tu, J. (2000). Development and validation of the Osteoporosis Risk Assessment Instrument to facilitate selection of women for bone densitometry. *CMAJ* **162**, 1289.

Campo, V. L., Kawano, D. F., Silva, D. B. D., Jr., and Carvalho, I. (2009). Carrageenans: Biological properties, chemical modifications and structural analysis—A review. *Carbohydr. Polym.* **77**, 167–180.

Cha, S. H., Ko, S. C., Kim, D., and Jeon, Y. J. (2010). Screening of marine algae for potential tyrosinase inhibitor: Those inhibitors reduced tyrosinase activity and melanin synthesis in zebrafish. *J. Dermatol.* **37**, 1–10.

Christiansen, C. (1993). Skeletal osteoporosis. *J. Bone Miner. Res.* **8**, S475–S480.

Curat, C., Wegner, V., Sengenes, C., Miranville, A., Tonus, C., Busse, R., and Bouloumie, A. (2006). Macrophages in human visceral adipose tissue: Increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* **49**, 744–747.

Das, S. K., Ren, R., Hashimoto, T., and Kanazawa, K. (2010). Fucoxanthin induces apoptosis in osteoclast-like cells differentiated from RAW264.7 cells. *J. Agric. Food Chem.* **58**, 6090–6095.

Dennis, C. L., Fung, K., Grigoriadis, S., Robinson, G. E., Romans, S., and Ross, L. (2007). Traditional postpartum practices and rituals: A qualitative systematic review. *Womens Health* **3**, 487–502.

Dettmar, P. W., Strugala, V., and Craig Richardson, J. (2011). The key role alginates play in health. *Food Hydrocoll.* **25**, 263–266.

ElHage, A. (2005). Hazardous to Teen Health. North Carolina Family Policy Council, North Carolina, USA, pp. 1–4.

Ellerker, A. (1955). Breast cancer in hypothyroid subjects. *Proc. R. Soc. Med.* **48**, 554–560.

Fujita, T., Ohue, T., Fujii, Y., Miyauchi, A., and Takagi, Y. (1996). Heated oyster shell-seaweed calcium (AAA Ca) on osteoporosis. *Calcif. Tissue Int.* **58**, 226–230.

Funahashi, H., Imai, T., Tanaka, Y., Tsukamura, K., Hayakawa, Y., Kikumori, T., Mase, T., Itoh, T., Nishikawa, M., and Hayashi, H. (1999). Wakame seaweed suppresses the proliferation of 7, 12-dimethylbenz (a)-anthracene-induced mammary tumors in rats. *Cancer Sci.* **90**, 922–927.

Funahashi, H., Imai, T., Mase, T., Sekiya, M., Yokoi, K., Hayashi, H., Shibata, A., Hayashi, T., Nishikawa, M., and Suda, N. (2001). Seaweed prevents breast cancer? *Cancer Sci.* **92**, 483–487.

Geyer, C., Forster, J., Lindquist, D., Chan, S., Romieu, C., Pienkowski, T., Jagiello-Gruszfeld, A., Crown, J., Chan, A., and Kaufman, B. (2006). Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N. Engl. J. Med.* **355**, 2733.

Hannan, M. T., Felson, D. T., Dawson-Hughes, B., Tucker, K. L., Cupples, L. A., Wilson, P. W. F., and Kiel, D. P. (2000). Risk factors for longitudinal bone loss in elderly men and women: The Framingham Osteoporosis Study. *J. Bone Miner. Res.* **15**, 710–720.

Heo, S. and Jeon, Y. (2009). Protective effect of fucoxanthin isolated from Sargassum siliquastrum on UV-B induced cell damage. *J. Photochem. Photobiol. B Biol.* **95**, 101–107.

Heo, S., Ko, S., Cha, S., Kang, D., Park, H., Choi, Y., Kim, D., Jung, W., and Jeon, Y. (2009a). Effect of phlorotannins isolated from Ecklonia cava on melanogenesis and their protective effect against photo-oxidative stress induced by UV-B radiation. *Toxicol. In Vitro* **23**, 1123–1130.

Heo, S. J., Hwang, J. Y., Choi, J. I., Han, J. S., Kim, H. J., and Jeon, Y. J. (2009b). Diphlorethohydroxycarmalol isolated from Ishige okamurae, a brown algae, a potent α-glucosidase and α-amylase inhibitor, alleviates postprandial hyperglycemia in diabetic mice. *Eur. J. Pharmacol.* **615**, 252–256.

Heo, S. J., Ko, S. C., Kang, S. M., Cha, S. H., Lee, S. H., Kang, D. H., Jung, W. K., Affan, A., Oh, C., and Jeon, Y. J. (2010). Inhibitory effect of diphlorethohydroxycarmalol on melanogenesis and its protective effect against UV-B radiation-induced cell damage. *Food Chem. Toxicol.* **48**, 1355–1361.

Huggins, C., Grand, L., and Brillantes, F. (1961). Mammary cancer induced by a single feeding of polynuclear hydrocarbons, and its suppression. *Nature* **189**, 204–207.

Kang, H., Kim, H., Byun, D., Son, B., Nam, T., and Choi, J. (2004). Tyrosinase inhibitors isolated from the edible brown alga Ecklonia stolonifera. *Arch. Pharm. Res.* **27**, 1226–1232.

Kanis, J., Delmas, P., Burckhardt, P., Cooper, C., and Torgerson, D. (1997). Guidelines for diagnosis and management of osteoporosis. *Osteoporos. Int.* **7**, 390–406.

Kaplan-Myrth, N. and Dollin, J. (2007). Cervical cancer awareness and HPV prevention in Canada. *Can. Fam. Physician* **53**(693–696), 697.

Kelishadi, R. (2007). Childhood overweight, obesity, and the metabolic syndrome in developing countries. *Epidemiol. Rev.* **29**, 62–76.

Khan, S., Kong, C., Kim, J., and Kim, S. (2010). Protective effect of Amphiroa dilatata on ROS induced oxidative damage and MMP expressions in HT1080 cells. *Biotechnol. Bioprocess Eng.* **15**, 191–198.

Kim, S. and Wijesekara, I. (2010). Development and biological activities of marine-derived bioactive peptides: A review. *J. Funct. Foods* **2**, 1–9.

Kong, C. S., Kim, J. A., Yoon, N. Y., and Kim, S. K. (2009). Induction of apoptosis by phloroglucinol derivative from Ecklonia Cava in MCF-7 human breast cancer cells. *Food Chem. Toxicol.* **47**, 1653–1658.

Kramer, M. and Wells, C. (1996). Does physical activity reduce risk of estrogen-dependent cancer in women? *Med. Sci. Sports Exerc.* **28**, 322.

Lahaye, M. (1991). Marine algae as sources of fibres: Determination of soluble and insoluble dietary fibre contents in some lsquosea vegetablesrsquo. *J. Sci. Food Agric.* **54**, 587–594.

Lehtinen, M. and Dillner, J. (2002). Preventive human papillomavirus vaccination. *Sex. Transm. Infect.* **78**, 4–6.

Maeda, H., Hosokawa, M., Sashima, T., Funayama, K., and Miyashita, K. (2005). Fucoxanthin from edible seaweed, Undaria pinnatifida, shows antiobesity effect through UCP1 expression in white adipose tissues. *Biochem. Biophys. Res. Commun.* **332**, 392–397.

Maeda, H., Hosokawa, M., Sashima, T., and Miyashita, K. (2007). Dietary combination of fucoxanthin and fish oil attenuates the weight gain of white adipose tissue and decreases blood glucose in obese/diabetic KK-Ay mice. *J. Agric. Food Chem.* **55**, 7701–7706.

Majem, L., Tresserras, R., Canela, J., and Salleras, L. (1988). Dietary iodine deficiency and breast cancer mortality: An ecological study. *Int. J. Epidemiol.* **17**, 686–687.

Miyashita, K. and Hosokawa, M. (2009). Anti–obesity Effect of Allenic Carotenoid, Fucoxanthin. Nutrigenomics and Proteomics in Health and Disease: Impact of Food Factors–Gene Interactions. Wiley–Blackwell Publisher, Ames, IA, pp. 145–160.

Moo-Puc, R., Robledo, D., and Freile-Pelegrin, Y. (2009). In vitro cytotoxic and antiproliferative activities of marine macroalgae from Yucatán, Mexico. *Cienc. Mar.* **35**, 345–358.

Moore, M. A., Park, C. B., and Tsuda, H. (1998). Soluble and insoluble fiber influences on cancer development. *Crit. Rev. Oncol. Hematol.* **27**, 229–242.

Munoz, N., Bosch, F. X., de Sanjose, S., Herrero, R., Castellsague, X., Shah, K. V., Snijders, P. J., and Meijer, C. J. (2003). Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N. Engl. J. Med.* **348**, 518–527.

Nieves, J. W., Formica, C., Ruffing, J., Zion, M., Garrett, P., Lindsay, R., and Cosman, F. (2005). Males have larger skeletal size and bone mass than females, despite comparable body size. *J. Bone Miner. Res.* **20**, 529–535.

Ortiz, J., Romero, N., Robert, P., Araya, J., Lopez-Hernandez, J., Bozzo, C., Navarrete, E., Osorio, A., and Rios, A. (2006). Dietary fiber, amino acid, fatty acid and tocopherol contents of the edible seaweeds Ulva lactuca and Durvillea antarctica. *Food Chem.* **99**, 98–104.

Paczos, T., Liu, W., and Chen, F. (2010). Human papillomavirus vaccine: A comprehensive review. *N. A. J. Med. Sci.* **3**, 201–204.

Pangestuti, R. and Kim, S. K. (2011). Neuroprotective effects of marine algae. *Mar. Drugs* **9**, 803–818.

Panlasigui, L., Baello, O., Dimatangal, J., and Dumelod, B. (2003). Blood cholesterol and lipid-lowering effects of carrageenan on human volunteers. *Asia Pac. J. Clin. Nutr.* **12**, 209–214.

Parkin, D. (2001). Global cancer statistics in the year 2000. *Lancet Oncol.* **2**, 533–543.
Parkin, D., Pisani, P., and Ferlay, J. (1999). Global cancer statistics. *CA Cancer J. Clin.* **49**, 33–64.
Parkin, D., Bray, F., Ferlay, J., and Pisani, P. (2002). Global cancer statistics, 2002. *CA Cancer J. Clin.* **55**, 74.
Pelkman, C., Navia, J., Miller, A., and Pohle, R. (2007). Novel calcium-gelled, alginate-pectin beverage reduced energy intake in nondieting overweight and obese women: Interactions with dietary restraint status. *Am. J. Clin. Nutr.* **86**, 1595–1692.
Pettigrew, R. and Hamilton-Fairley, D. (1997). Obesity and female reproductive function. *Br. Med. Bull.* **53**, 341–358.
Pisani, P., Bray, F., and Parkin, D. (2002). Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. *Int. J. Cancer* **97**, 72–81.
Popkin, B. and Doak, C. (1998). The obesity epidemic is a worldwide phenomenon. *Nutr. Rev.* **56**, 106–114.
Pujol, C., Carlucci, M., Matulewicz, M., and Damonte, E. (2007). Natural sulfated polysaccharides for the prevention and control of viral infections. *In* ''Bioactive Heterocycles V'', (M. Khan, Ed.), pp. 259–281. Springer, Berlin/Heidelberg.
Ranathunga, S., Rajapakse, N., and Kim, S. K. (2006). Tyrosinase inhibitory flavonoid glycoside derived from an edible brown alga, Hizikia fusiformis and its structure-activity relationships. *Marin baio Tekunoroji Gakkai Taikai Koen Youshishu* **9**, 133.
Rennie, K. and Jebb, S. (2005). Prevalence of obesity in Great Britain. *Obes. Rev.* **6**, 11–12.
Riggs, B., Melton, L., III, Robb, R., Camp, J., Atkinson, E., Peterson, J., Rouleau, P., McCollough, C., Bouxsein, M., and Khosla, S. (2004). Population-based study of age and sex differences in bone volumetric density, size, geometry, and structure at different skeletal sites. *J. Bone Miner. Res.* **19**, 1945–1954.
Riggs, B. L., Melton, L., III, Robb, R. A., Camp, J. J., Atkinson, E. J., McDaniel, L., Amin, S., Rouleau, P. A., and Khosla, S. (2008). A population-based assessment of rates of bone loss at multiple skeletal sites: Evidence for substantial trabecular bone loss in young adult women and men. *J. Bone Miner. Res.* **23**, 205–214.
Roberts, J. N., Buck, C. B., Thompson, C. D., Kines, R., Bernardo, M., Choyke, P. L., Lowy, D. R., and Schiller, J. T. (2007). Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. *Nat. Med.* **13**, 857–861.
Ruperez, P. and Saura-Calixto, F. (2001). Dietary fibre and physicochemical properties of edible Spanish seaweeds. *Eur. Food Res. Technol.* **212**, 349–354.
Schiller, J. T. and Davies, P. (2004). Delivering on the promise: HPV vaccines and cervical cancer. *Nat. Rev. Microbiol.* **2**, 343–347.
Schuit, S. C. E., van der Klift, M., Weel, A. E. A. M., de Laet, C. E. D. H., Burger, H., Seeman, E., Hofman, A., Uitterlinden, A. G., van Leeuwen, J. P. T. M., and Pols, H. A. P. (2004). Fracture incidence and association with bone mineral density in elderly men and women: The Rotterdam Study. *Bone* **34**, 195–202.
Shahidi, F. (2008). Bioactives from Marine Resources. ACS Publications, Washington, pp. 24–34.
Shahidi, F. and Janak Kamil, Y. (2001). Enzymes from fish and aquatic invertebrates and their application in the food industry. *Trends Food Sci. Technol.* **12**, 435–464.
Shimoda, H., Tanaka, J., Shan, S., and Maoka, T. (2010). Anti-pigmentary activity of fucoxanthin and its influence on skin mRNA expression of melanogenic molecules. *J. Pharm. Pharmacol.* **62**, 1137–1145.
Skibola, C. (2004). The effect of Fucus vesiculosus, an edible brown seaweed, upon menstrual cycle length and hormonal status in three pre-menopausal women: A case report. *BMC Complement. Altern. Med.* **4**, 1–8.
Skibola, C., Curry, J., VandeVoort, C., Conley, A., and Smith, M. (2005). Brown kelp modulates endocrine hormones in female Sprague-Dawley rats and in human luteinized granulosa cells. *J. Nutr.* **135**, 296.

Solano, F., Briganti, S., Picardo, M., and Ghanem, G. (2006). Hypopigmenting agents: An updated review on biological, chemical and clinical aspects. *Pigment Cell Res.* **19**, 550–571.

Stice, E., Maxfield, J., and Wells, T. (2003). Adverse effects of social pressure to be thin on young women: An experimental investigation of the effects of ''fat talk''. *Int. J. Eat. Disord.* **34**, 108–117.

Swing, J. (2003). What future for the oceans? *Foreign Aff.* **82**, 139–152.

Teas, J., Harbison, M., and Gelman, R. (1984). Dietary seaweed (Laminaria) and mammary carcinogenesis in rats. *Cancer Res.* **44**, 2758.

Teas, J., Hurley, T., Hebert, J., Franke, A., Sepkovic, D., and Kurzer, M. (2009). Dietary seaweed modifies estrogen and phytoestrogen metabolism in healthy postmenopausal women. *J. Nutr.* **139**, 939.

Trayhurn, P. and Wood, I. S. (2005). Signalling role of adipose tissue: Adipokines and inflammation in obesity. *Biochem. Soc. Trans.* **33**, 1078–1081.

Wang, C., Huang, C., Hu, C., and Chan, H. (1997). The effect of glycolic acid on the treatment of acne in Asian skin. *Dermatol. Surg.* **23**, 23–29.

Witvrouw, M. and De Clercq, E. (1997). Sulfated polysaccharides extracted from sea algae as potential antiviral drugs. *Gen. Pharmacol.* **29**, 497–511.

Yoon, N., Eom, T., Kim, M., and Kim, S. (2009). Inhibitory effect of phlorotannins isolated from Ecklonia cava on mushroom tyrosinase activity and melanin formation in mouse B16F10 melanoma cells. *J. Agric. Food Chem.* **57**, 4124–4129.

Yuan, Y. and Walsh, N. (2006). Antioxidant and antiproliferative activities of extracts from a variety of edible seaweeds. *Food Chem. Toxicol.* **44**, 1144–1150.

Yuan, Y. V., Carrington, M. F., and Walsh, N. A. (2005). Extracts from dulse (Palmaria palmata) are effective antioxidants and inhibitors of cell proliferation in vitro. *Food Chem. Toxicol.* **43**, 1073–1081.

Zhang, Y. Q., Tsai, Y. C., Monie, A., Hung, C. F., and Wu, T. C. (2010). Carrageenan as an adjuvant to enhance peptide-based vaccine potency. *Vaccine* **28**, 5212–5219.