CHAPTER 14

Potential Beneficial Effects of Marine Algal Sterols on Human Health

Se-Kwon Kim[*,†,1] and **Quang Van Ta**[†]

Contents

Abstract

The importance of bioactive derivatives as functional ingredients has been well recognized due to their valuable health beneficial effects. Therefore, isolation and characterization of novel functional ingredients with biological activities from marine algae have gained much attention. Sterols are important structural component of cell membranes. It has been reported that plant sterols exhibit various beneficial biological activities such as hypercholesterolemic, antioxidant, anticancer, antidiabetic, antihypertensive, anti-inflammatory, antifungal, and antibacterial activities. Marine algae

* Marine Bioprocess Research Center, Pukyong National University, Busan, Republic of Korea
† Marine Biochemistry Laboratory, Department of Chemistry, Pukyong National University, Busan, Republic of Korea
[1] Corresponding author: Se-Kwon Kim, *E-mail address:* sknkim@pknu.ac.kr

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with a great diversity can be a very interesting natural resource of sterols. This chapter focuses on biological activities of marine algae derived sterols with potential health beneficial applications in functional foods and pharmaceuticals.

I. INTRODUCTION

Sterols are an important family of lipids, present in the majority of eukaryotic cells and they are categorized to the steroids group, which also contain the same fused four-ring core structure and have different biological roles as hormones and signaling molecules. In addition, sterols have a hydroxyl group at the 3-position of the A-ring. This hydroxyl group is the polar group in the structure; the rest of aliphatic chain is nonpolar. Sterols are essential components of the membranes of all eukaryotic organisms, controlling membrane fluidity and permeability. Sterols are highly diverse in nature. Their composition depends on the environment and on specificity of the organism. Because of different routes of synthesis, sterols from plants, fungi, and animals show marked differences. Sterols are synthesized from the common precursor squalene. A cytochrome P450 enzyme belonging to CYP51 class catalyzes the synthesized process. P450 enzyme used intermediated substrate lanosterol for synthesize sterol in animals, fungi, and stramenopiles. Moreover, plant sterols are synthesized from intermediate substrate, obtusifoliol (Fahy *et al*., 2005; Gaulin *et al*., 2010; Kamenarska *et al*., 2006).

Plant sterols have been shown to inhibit uptake of both dietary and endogenous produced (biliary) cholesterol from the intestine. Clinical studies have demonstrated that sterols had ability in lowering ''bad'' low-density lipoprotein cholesterol (LDL-C) levels. In addition, plant sterols did not have effect on ''healthy'' high-density lipoprotein cholesterol (HDL-C) and triacylglycerol levels. Moreover, clinical studies have showed that plant sterols could reduce the risk of heart disease by prevention and reduction of hypercholesterolemia. Several studies have indicated that phytosterols may have health-promoting effects such as anticancer activity. Studies on cellular base models showed that plant sterols were toxic to breast cancer, colon cancer, and prostate cancer cells. Additionally, plan sterols have been suggested that they have anti-inflammatory, antibacterial and antifungal activities. Further, long-term studies on animal models and humans did not show toxicity effect of plant sterols (Moreau *et al*., 2002).

Sterols also can be found in marine algae. It has been reported that brown algae (Phaeophyceae) contain mainly fucosterol and fucosterol derivatives, red algae (Rhodophyceae) contain mainly cholesterol and cholesterol derivatives, and green algae (Chlorophyceae) contain mainly

ergosterol and 24-ethylcholesterol (Sánchez-Machado *et al*., 2004). Hence, the search for natural bioactive sterols as safe alternatives from marine algae is important in the food industry. This chapter focuses on potential benefits of marine algae-derived sterols on human health.

II. POTENTIAL HEALTH BENEFITS OF STEROLS FROM MARINE ALGAE

A. Antibacterial activity

Tuberculosis is the second commonest cause of death worldwide. Thirty-two percent of the world's population is infected with *Mycobacterium tuberculosis*, the main cause of tuberculosis. Most forms of active tuberculosis can be treated with 6 months of medication. Unfortunately, outbreaks of multidrug resistant tuberculosis have been occurring since 1990s. Natural products form one avenue in the search for new antituberculosis agents. Recently, marine algae have become targets for screening in search of novel compounds of potential medical value. It has been reported that saringosterol had been isolated from brown algae *Sargassum ringgoldianum* and had antitubercular activity (Ikekawa *et al*., 1968). Its minimum inhibition concentration (MIC) against *M. tuberculosis* H_{37}Rv was determined as 0.25 μg/ml, which is the lowest value found for plant-derived natural products, compare to the tuberculosis drug rifampicin that was determined as 0.25 μg/ml of MIC in same assay. In addition, low concentration of saringosterol showed no toxicity against in the monkey kidney epithelial (Vero) cells. Sargosterol showed half maximal inhibitory concentration (IC_{50}) of RS mg/ml on Vero cells. The sargosterol isolated from *Lessonia nigrescens* are both 1:1 mixture of 24*S* and 24*R* epimers. Individual isomers were separated by normal-phase high-performance liquid chromatography (HPLC). In the antitubercular assay, the 24*R* isomer was found eight times more active against *M. tuberculosis* H_{37}Rv with MIC of 0.125 μg/ml than that of the 24*S* isomer which had a MIC of 1 μg/ml. Saringosterol could be considered as an excellent lead compound due to its activity, specificity, and low toxicity (Wächter *et al*., 2001). Recently, 15 algae extracts were screened antibacterial activity and it was found that extracts from *Isochrysis galbana* inhibited multidrug resistant (MDR) *M. tuberculosis*. Screening on seven isolated MDR *M. tuberculosis*, which resisted more than three antibacterial drugs, extract from *I. galbana* showed the MIC of 50 μg/ml compare to those of the tuberculosis drugs rifampicin (40 μg/ml), amikacin (700 μg/ml), streptomycin (4 μg/ml), ρ-amino salicylic acid (2.5 μg/ml), and isoniazid (0.2 μg/ml). Thirteen unsaturated sterols with three major sterols such as 24-oxocholesterol acetate, ergost-5-en-3 β-ol, and cholest-5-24-1,3-(acetyloxy)-,3β-ol have been purified (Prakash *et al*., 2010).

This finding indicated the presences of sterols may have effect on MDR *M. tuberculosis*. Therefore, marine algal sterols have potential in the development of urgently needed tuberculosis drugs.

B. Antioxidant activity

The deterioration of some foods has been identified due to oxidation of lipids or rancidity and formation of undesirable secondary lipid peroxidation products. Lipid oxidation by reactive oxygen species (ROS) such as superoxide anion, hydroxyl radicals, and H_2O_2 also causes a decrease in nutritional value of lipid foods and affects their safety and appearance. In the food and the pharmaceutical industries, many synthetic commercial antioxidants such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), *tert*-butylhydroquinone (TBHQ), and propyl gallate (PG) have been used to retard the oxidation and the peroxidation processes. However, the use of these synthetic antioxidants must be under strict regulation due to potential health hazards (Hettiarachchy *et al.*, 1996; Park *et al.*, 2001). Hence, the search for natural antioxidants as safe alternatives from natural resources such as marine algae is important in the food industry. Fortunately, it was reported that fucosterol isolated from marine algae *Pelvetia siliquosa* had antioxidant activity. Rats were treated with fucosterol at dose of 30 mg/kg/day for 7 days, prior the administration of carbon tetrachloride (CCl_4). Fucosterol causes a significant elevation of free radical scavenging enzyme activities such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GSH-px). Increase in the catalase activity with respect to CCl_4 treatment indicated that fucosterol could play an important role in scavenging hydrogen peroxide. Elevation of SOD activity indicated that fucosterol could help in cellular defense mechanism by preventing cell membrane oxidation. In addition, the increase in glutathione peroxidase activity indicated that fucosterol also helped in the restoration of vital molecules such as cytochrome, glutathione. The results showed that sterol have antioxidant activity on rat model (Lee *et al.*, 2003). Hence, fucosterol can be used as potential antioxidants in the food industry.

C. Anticancer activity

Some of the marine algae and their secondary metabolites have shown promising anticancer activities, and hence, they are important sources to manufacture novel anticancer drugs. Sheu *et al.* (1997) had shown that sterols from brown alga *Turbinaria ornata* have cytotoxicity effect on P-388 (mouse lymphocytic leukemia) cells, KB (human mouth epidermoid carcinoma) cells, and HT-29 (human colon carcinoma) cells. Oxygenated fucosterol from *Turbinaria conoides* also has cytotoxic effect on cancer

cells (Sheu *et al*., 1999). Moreover, new sterols from *Sargassum carpophyllum* have shown cytotoxic effect on human promyelocytic leukemia HL-60 cells (Tang *et al*., 2002). It has also been reported that oxysterol from red alga *Jania rubens* showed an ID_{50} value of 0.5 μg/ml toward KB cells (Ktari *et al*., 2000). Recently, two sterols glycoside isolated from red alga *Peyssonnelia* sp. displayed moderate activity toward human cancer cell lines (Lin *et al*., 2010). These compounds displayed significant cytotoxicity toward human breast cancer MDA-MB-468 cells and human lung cancer cell line A549 with $IC_{50} = 0.71$ and 0.86 μM, respectively, which were often more resistant to cytotoxins than those of other common cancer cells that inhibited with $IC_{50} = 0.93$ and 0.97 μM. Collectively sterols from marine algae have a promising potential to be used as valuable chemopreventive agents in cancer therapy.

D. Antidiabetic activity

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose levels. Diabetes without proper treatments can cause many complications. Acute complications include hypoglycemia, diabetic ketoacidosis, or nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, chronic renal failure, and retinal damage. Hence, antidiabetic agents are urgently required. It has been reported that fucosterol from *P. siliquosa* have antidiabetic activity. Fucosterol at a dose of 100 and 300 mg/kg reduced hyperglycemic effect by 25–33% in epinephrine-induced diabetes mouse model. Moreover, fucosterol at a dose of 100 and 300 mg/kg was shown to decrease the glycogen degradation of mouse liver by 23–29%. Hence, it was suggested that fucosterol from marine alga *P. siliquosa* has potential in development of antidiabetic agent (Lee *et al*., 2004).

E. Antihypertensive and antihypercholesterolemic activities

Angiotensin-I-converting enzyme (ACE) plays an important physiological role in regulation of blood pressure by converting angiotensin I to angiotensin II, a potent vasoconstrictor. Further, ACE is implicated in cell oxidative stress, augmenting the generation of ROS and peroxynitrite and also in thrombosis, during which induces platelet activation, aggregation, and adhesion (McFarlane *et al*., 2003). Inhibition of ACE is considered to be a useful therapeutic approach in the treatment of hypertension. Therefore, in the development of drugs to control high blood pressure, ACE inhibition has become an important activity. Many studies have been attempted in the synthesis of ACE inhibitors such as captopril, enalapril, alcacepril, and lisinopril, which are currently used in the treatment of hypertension and heart failure in human. However, these synthetic drugs

are believed to have certain side effects such as cough, taste disturbances, skin rashes, or angioneurotic edema and all of which might be intrinsically linked to synthetic ACE inhibitors. The search for natural ACE inhibitors as alternatives to synthetic drugs is of great interest to prevent several side effects (Atkinson and Robertson, 1979). Fucosterol was reported as safety agent on animal models. The modulation of ACE levels was studied using fucosterol in cultured bovine carotid endothelial cells. Dexamethasone was treated to elevate the levels of ACE in the cells. After adding fucosterol to the culture medium, the activity of ACE in endothelial cells has decreased; however, fucosterol did not directly inhibit ACE activity. It has been found that fucosterol lowers the ACE levels in endothelial cells by inhibiting the synthesis of glucocorticoid receptors involved in the regulation of ACE levels (Hagiwara *et al*., 1986).

LDL-C is called ''bad'' cholesterol because elevated level of LDL cholesterol is associated with an increased risk of coronary heart disease. LDL lipoprotein deposits cholesterol on the artery walls, causing the formation of a hard, thick substance called cholesterol plaque. Over the time, cholesterol plaque causes thickening of the artery walls and narrowing of the arteries, a process called atherosclerosis. In contrast, HDL cholesterol is called the ''good cholesterol'' because it prevents atherosclerosis by extracting cholesterol from the artery walls and disposing them through the liver. The highest HDL-C level gives the greater capacity to remove cholesterol and prevent dangerous blockages from developing in blood vessels. HDL-C helps to keep blood vessels widened (dilated), thereby promoting better blood flow. HDL-C also reduces blood vessel injury through its antioxidant and anti-inflammatory functions, among other effects (Toth, 2005). Plant sterols have been reported as agents that can reduce the risk of heart disease by lowering LDL-C levels. Therefore, it suggested that marine algal sterols could be used to prevent cardiovascular diseases. According to Plaza *et al*. (2008), sterols from several edible marine algae, such as *Himanthalia elongate*, *Undaria pinnatifida*, *Phorphyra* spp., *Chondus crispus*, *Cystoseira* spp., *Ulva* spp., have potential effect on reducing the total and LDL-C level. In addition, 4-methylsterols from *Crypthecodinium cohnii* had no effect on any serum or liver lipid parameter. However, the percentage of serum HDL-C level was increased by 25%. Addition of bile salt to a cholesterol containing diet raises the serum and the liver cholesterol levels. Rats fed with cholesterol diet and cholesterol plus bile salt have shown significant increase in total serum cholesterol and decreased HDL-C level. Moreover, cholesterol-bile salt plus 4-methylsterols significantly raised the amount of HDL-C and triglyceride levels, but no other serum or liver lipid parameters were affected (Kritchevsky *et al*., 1999). These effects have shown the potential application of fucosterols in the prevention of risk of cardiovascular diseases.

III. CONCLUSIONS

Marine algae-derived functional ingredients play a vital role in human health and nutrition. Increasing knowledge on marine algal bioactive compounds has raised the demand for novel functional food ingredients and pharmaceuticals. Hence, sterols from marine algae can be used as functional ingredients to reduce chronic diseases in human body. However, there are few studies on marine algal sterols compared with those of plant sterols. Therefore, the future studies on marine sterols will lead more beneficial sterols bioactive compounds. Collectively, the sterols, which derived from marine algae, have potential to expand its health beneficial value not only in the food industry but also in the pharmaceutical industry.

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