CHAPTER 15

Laminaria japonica as a Food for the Prevention of Obesity and Diabetes

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Contents

Abstract

Various seaweeds have traditionally been used as flavoring materials, food additives, and foodstuffs in many countries, especially those in Asia. The seaweed *Laminaria japonica* (LJ) is popular as "kombu" in Japanese cuisine. *Laminaria* sp. is one of the most important marine medicinal foodstuffs, as its biological functions have been widely investigated in both *in vitro* and *in vivo* experiments. This chapter introduces recent reports on the ability of *Laminaria* to prevent obesity and diabetes, and some approaches for effectively using the bioactivities found in *Laminaria*. The inhibitory effects of *Laminaria* sp. on triglyceride absorption were investigated in triglyceride-loaded mice and in mice with high-fat-diet-induced obesity. Shaved *Laminaria*, known as "tororokombu," showed more effective activities in

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these experiments. The active component was considered to be alginic acid in the water-soluble fraction. On the other hand, the antihyperglycemic effects of a hot water extract of immature *Laminaria* were investigated in carbohydrate-loaded mice and in *in vitro* experiments using Caco-2 cells. The potential usefulness of *Laminaria* sp. as marine medicinal foods may be increased through the use of different processing methods and/or growth stages. These reports suggest that LJ may be useful for preventing lifestyle-related diseases.

I. INTRODUCTION

Many types of seaweed are commonly consumed as food worldwide. Seaweeds have been established as healthy food materials that are rich in minerals and dietary fibers. Especially, *Laminaria japonica* (LJ) ''kombu,'' *Undaria pinnatifida* ''wakame,'' *Gelidium crinale* ''tengusa,'' and *Cladosiphon okamuranus* ''mozuku'' have traditionally been consumed in Japan. In addition, seaweeds have been harvested or cultivated, especially in Asia, as a source of alginate, agar, and carrageenan, that is, gelatinous substances, for various industrial applications. *Laminaria* sp. contain soluble fibers such as alginate and fucoidan, as well as fat-soluble components such as fucoxanthin and fucosterol (Mizuno *et al.*, 2009; Stevan *et al.*, 2001; Zhang *et al.*, 2008), in addition to being particularly rich in minerals such as magnesium, iodine, calcium, iron, and zinc.

Recently, seaweeds have been attracting attention as healthy foods that contain beneficial components, which may be useful for the prevention and treatment of lifestyle-related diseases. Thus far, extracts of *Laminaria* sp. have been reported to exhibit anticancer (Reddy *et al.*, 1985; Yamamoto and Maruyama, 1985), antioxidative (Reddy *et al.*, 1984), antiviral (Makarenkova *et al.*, 2010), antiatherogenic (Matanjun *et al.*, 2010), immunostimulatory (Jeong *et al.*, 2006; Oomizu *et al.*, 2006), and anti-inflammatory (Shiratori *et al.*, 2005) effects. The modern tendency to consume nutritionally rich diets coupled with irrational dietary habits has contributed to the growth of lifestyle-related diseases such as obesity and diabetes.

In this chapter, the antiobesity and the antidiabetic effects of *Laminaria* sp. are described. The latest research on the biological activity found in LJ is introduced.

II. ANTIOBESITY EFFECTS

A. Obesity

Obesity is an abnormal condition in which excessive triglycerides (TGs) accumulate in the adipose tissue. Obesity has reached epidemic proportions globally, and the World Health Organization estimates that there are

more than 1 billion overweight adults, of whom at least 300 million are obese. Economic growth and the modernization, urbanization, and globalization of food markets are some of the elements that have contributed to the obesity epidemic. Obesity is the most important risk factor for lifestyle-related diseases such as hypertension, type 2 diabetes, and hyperlipidemia (Golay and Ybarra, 2005; Matsuzawa *et al*., 1995). In particular, obesity causes an imbalance in the level of adipocytokines secreted by adipocytes, such as leptin, adiponectin, resistin, and plasminogen activator inhibitor-1, due to the excessive accumulation of visceral fat and can cause metabolic syndrome (Matsuzawa, 2006; You *et al*., 2005).

The plasma TG level is also related to cardiovascular disease (Hokanson and Austin, 1996), and a high postprandial TG level is a risk factor for atherosclerotic disease. Patients with hypertriglyceridemia tend to have prolonged postprandial hypertriglyceridemia after a high-fat diet (HFD) (Patsch *et al*., 1992). An excess postprandial hypertriglyceridemia response indicates poor TG clearance from the bloodstream and is often associated with atherosclerosis, insulin resistance, and obesity (Gott, 1998). Thus, the prevention of postprandial hypertriglyceridemia is very important for a healthy life.

B. Antiobesity effects of seaweeds

Over the past few decades, several studies have focused on fucoxanthin contained in seaweed. Fucoxanthin, a characteristic carotenoid of brown algae, has a unique structure that includes an unusual allenic bond and 5,6-monoepoxide. Wakame (*U. pinnatifida*), an edible seaweed, is rich in fucoxanthin.

Maeda *et al*. (2005) reported that fucoxanthin has an antiobesity effect by modifying uncoupling protein 1 (UCP1) expression in white adipose tissue (WAT) in KKAy mice, an animal model of type 2 diabetes with obesity. When fucoxanthin is orally administered to mice, it is metabolized to fucoxanthinol, which is further converted into amarouciaxanthin A (Asai *et al*., 2004; Sugawara *et al*., 2002). Fucoxanthin and its metabolite fucoxanthinol have been shown to reduce the expression of peroxisome proliferator-activated receptor (PPAR) γ in 3T3-L1 preadipocytes, which in turn inhibits differentiation to mature adipocytes (Maeda *et al*., 2006), suggesting that fucoxanthin inhibits adipocyte maturation and stimulates UCP1 expression in WAT.

In addition, Maeda *et al*. (2009) reported that fucoxanthin-rich wakame lipids (WLs) had antiobesity and antidiabetic effects on HFD-induced obesity in mice. The increased expression of monocyte chemoattractant protein-1 (MCP-1) mRNA in HF mice was normalized by ingestion of WL with a HFD. Moreover, the HF-WL diet may ameliorate alterations in lipid metabolism and insulin resistance induced by a HFD by promoting

the expression of β3-adrenergic receptor (Adrb3) mRNA in WAT and glucose transporter 4 (GLUT4) mRNA in skeletal muscle tissues. These results suggest that there is a biochemical and nutritional basis for the application of fucoxanthin-rich WLs for the treatment of obesity and diabetes-related disorders.

The effects of fucoxanthin-rich seaweed extract (Fx-SEE) on body weight gain and lipid metabolism in HF-fed C57BL/6J mice were investigated by Jeon *et al*. (2010). They demonstrated that Fx-SEE affects the plasma and hepatic lipid profile, fecal lipids, and body fat mass, and alters hepatic cholesterol metabolism, FA synthesis, and lipid absorption in mice.

The antiobesity and antidiabetic effects of some allenic compounds including fucoxanthin were reported by Miyashita *et al*. (2011). These compounds improved insulin resistance and decreased blood glucose levels through the regulation of cytokine secretions from WAT by inducing UCP1. The key structures of these activities were thought to be an allenic bond and two hydroxyl groups.

Some reports have focused on the alginate contained in seaweed. Sodium alginate from the brown seaweed *Laminaria digitata* (LD) is currently marketed as a weight-loss supplement, but its effects on gastric motor functions and satiation are unknown. Odunsi *et al*. (2010) clinically investigated the effects of 10 days of treatment with alginate or placebo on gastric function, satiation, appetite, and gut hormones associated with satiety in overweight or obese adults. They found that treatment with alginate for 10 days had no effect on any of the above parameters. These results suggested that the daily continuous intake of alginates may be required to prevent obesity.

''Tororokombu'' (TK) is a traditional Japanese food that is made by shaving *Laminaria* (kombu) very thinly. Miyata *et al*. (2009) first investigated the effects of NSK (non-shaved kombu) and TK on the absorption of TGs in the intestine by an oil-loading test in female SD rats (7 weeks old). One feature of this study is the improved efficiency of dissolution of the active component. SD rats were first divided into three groups: distilled water-treated, NSK-treated, and TK-treated groups. Next, corn oil (5 ml/kg) was administered orally. The elevation of the serum TG level in the NSK- and TK-treated groups was significantly lower than that in the normal rat group.

Next, the antiobesity effects of NSK and TK were investigated by a long-term experiment on obese female ddY mice (4 weeks old) induced by a HFD for 63 days. Mice were divided into four groups: ND (normal diet), HFD, HFD-NSK (HFD containing 3% NSK), and HFD-TK (HFD containing 3% TK) groups. The body weights on the 63rd day after treatment started and the serum TC levels in both the HFD-NSK and the HFD-TK groups were significantly lower than those in the HFD

group. The parauterus adipose tissue weight, and hepatic TG, serum TG, and TC levels in the HFD-TK group were significantly less than those in the HFD-NSK group. The fecal TG and TC levels in the HFD-TK group were significantly higher than those in the HFD group, and fecal TG in the HFD-TK-group was significantly higher than that in the HFD-NSK group. Consequently, it was demonstrated that TK consumption reduced the accumulation of visceral fat caused by HFD, and this effect of TK was more powerful than that of NSK, due to TG and cholesterol excretion in the feces. This report concluded that alginate may be one of the active components in *Laminaria* sp. In previous reports, alginate has been reported to have hypoglycemic and cholesterol-lowering effects by acting as a viscous soluble dietary fiber (Kimura *et al*., 1996; Pasquier *et al*., 1996; Paxman *et al*., 2008).

The inhibitory activities of NSK and TK against lipase were examined. The inhibitory activities of TK were greater than those of NSK, as shown in Fig. 15.1. In addition, TK had significantly higher alginate content than NSK, as shown in Fig. 15.2. The effects of extracted alginate with weak alkaline solution on lipase activity are shown in Fig. 15.3. Based on these results, alginate was thought to contribute to the inhibition of lipase. A lipase inhibitor should inhibit TG absorption and have an antiobesity effect *in vivo* (Miyata *et al*., 2009).

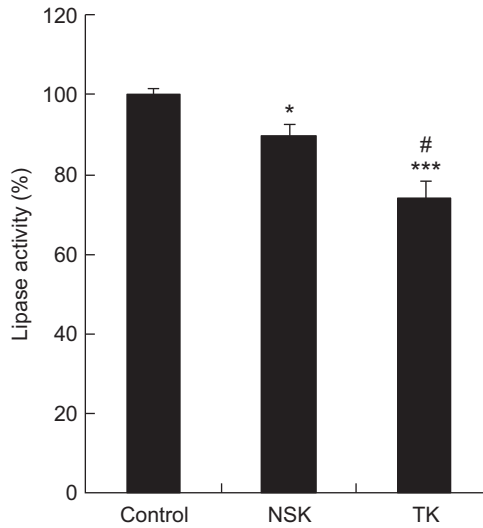

FIGURE 15.1 Effect of non-shaved kombu (NSK) and tororokombu (TK) on pancreatic lipase activity *in vitro*. Pancreatic lipase (from porcine) activity was measured using a Lipase Kit S according to the manufacturer's protocol. Data are presented as the mean ± SE ($n = 5$). $^{*}p < 0.05$, $^{***}p < 0.005$ versus control. $^{\#}p < 0.05$ NSK versus TK.

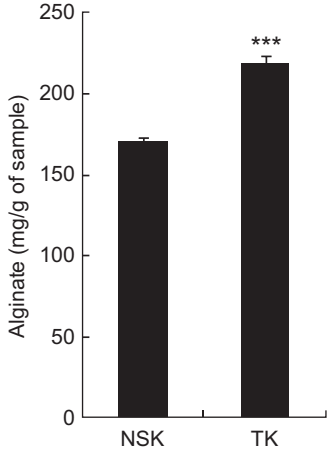

FIGURE 15.2 Alginate content eluted into weak alkaline solution from non-shaved kombu (NSK) and tororokombu (TK). The uronic acid content was analyzed using total components eluted from NSK and TK into phosphate-buffered saline (pH 8.0) for the determination of alginate by the carbazole method. Data are presented as the mean $\pm$ SE ($n = 3$). $^{***}p < 0.005$ versus NSK.

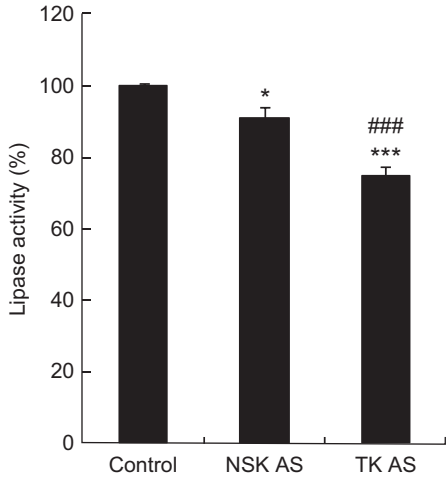

FIGURE 15.3 Effect of weak alkaline-soluble fraction (AS) from non-shaved kombu (NSK) and tororokombu (TK) on pancreatic lipase activity *in vitro*. Lipase activity was measured using a Lipase Kit S according to the manufacturer's protocol. Data are presented as the mean $\pm$ SE ($n = 5$). $^{*}p < 0.05$, $^{***}p < 0.005$ versus control, $^{\#\#\#}p < 0.005$ NSK AS versus TK AS.

These results suggest that TK, but not NSK, had an antiobesity effect. The shaving process alters the amount of active component that dissolves to cause physiological effects. The active component in the crude extract of *Laminaria* sp. can be considered to be an alginate.

III. ANTIDIABETIC EFFECTS

A. Diabetes

Diabetes mellitus is a group of metabolic diseases in which the patient has a high glucose level, either because the pancreas does not produce enough insulin (insulin secretory failure) or because the body does not respond to insulin that is produced (insulin resistance). The number of diabetes cases has been increasing worldwide in recent years. Most cases of diabetes mellitus can be classified into two types: type 1 and type 2. Type 1 diabetes is mainly related to genetic factors. On the other hand, type 2 diabetes is related to environmental factors including lack of exercise, high-calorie diet, obesity, stress, aging, and so on. Persistent hyperglycemia can lead to various complications including diabetic neuropathy, diabetic retinopathy, and diabetic nephropathy. Diabetes is a lifestyle-related disease that not only impairs the quality of life but also poses a threat to life.

To prevent or treat diabetes, stabilization of the blood glucose level is known to be effective. In general, to control the blood glucose level, it is important to reduce postprandial hyperglycemia primarily by inhibiting carbohydrate-digestive enzymes and/or delaying glucose absorption in the small intestine. Medications that inhibit α-glucosidase have been used clinically to treat diabetic patients (Krause *et al*., 1982; Nakamura, 2005; Sels *et al*., 1999).

B. Antidiabetic effects of seaweeds

Over the past few decades, several studies have focused on seaweeds as a source of potential bioactive materials.

Vaugelade *et al*. (2000) investigated the possible effects of algal polysaccharides on postprandial blood glucose and insulin responses in pig. Three seaweed fibers of different viscosities, extracted from *Palmaria palmata* (PP), *Eucheuma cottonii* (EC), or LD, were compared with purified cellulose (CEL). The addition of LD to the diet resulted in a dramatically reduced glucose absorption balance, accompanied by a higher amount of starch left in the small intestine. This study demonstrated that highly viscous alginates could affect the intestinal absorption of glucose and the insulin response.

Related studies on the bioactivity of LJ have also been reported. Jin *et al*. (2004) investigated the preventive effects of LJ aqueous extract (LJE) on alterations in the activity of hepatic xanthine oxidase and oxidative stress in streptozotocin-induced experimental diabetes. Pretreatment with LJE at 100 mg/kg orally for 5 days significantly reduced blood glucose levels and hepatic lipid peroxidation in diabetic rats due to the antioxidant activity of the extract.

The rhizoid of LJ is widely used in Chinese medicine as a treatment for diabetes. Bu *et al*. (2010) focused on the α-glucosidase inhibitor in the LJ rhizoid. This compound was determined to be butyl-isobutyl-phthalate (BIP) by spectral analysis. BIP exhibited significant concentration-dependent, noncompetitive inhibitory activity against α-glucosidase *in vitro*, with an IC_{50} of 38 μm. The ethyl acetate fraction (EAF) and purified BIP had a significant hypoglycemic effect in streptozotocin-induced diabetic mice *in vivo*. These results conclude that BIP could be considered an α-glucosidase inhibitor and may become an important agent for diabetes therapy.

During spring and summer, when LJ is cultivated in the waters surrounding Japan, much of the immature material is culled for density adjustment and disposed of as waste. This immature *Laminaria* may be a new abundant source of marine medicinal foods for preventing lifestyle-related diseases. The effects of LJE on the postprandial blood glucose level were examined in carbohydrate-loaded mice, as shown in Fig. 15.4.

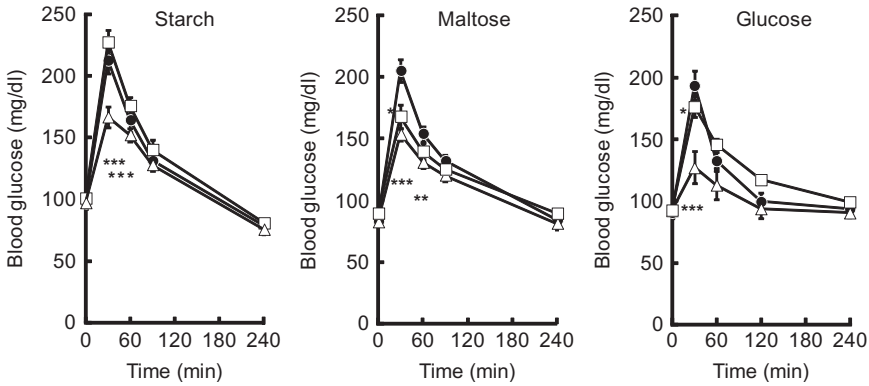

FIGURE 15.4 Effects of LJEs on postprandial elevation of the blood glucose level in carbohydrate-loaded mice. Carbohydrate (1000 mg/kg each) and sample solution were intubated to mice (1 ml/30 g BW). Sample solution contained distilled water only (control: closed circles), 640 mg/kg of mature LJE (mature LJ: open squares), or 640 mg/kg of immature LJE (immature LJ: open triangles). Data are expressed as the average ± SE ($n = 4$). $^{**}p < 0.01$, $^{***}p < 0.005$ versus control.

Mice were divided into three groups: distilled water-treated, immature LJ-treated, and mature LJ-treated groups. Next, carbohydrates (1000 mg/kg) were administered orally. When immature LJ (640 mg/kg) was administered orally simultaneously with starch (A), maltose (B), or glucose (C), the blood glucose levels at 30 min after administration were significantly suppressed ($p < 0.005$). LJE also had an antihyperglycemic effect in glucose-loaded mice and requires no enzymatic digestion for its absorption. Thus, the inhibitory action toward glucose absorption was evaluated by the measurement of remaining glucose in the small intestine. As shown in Fig. 15.5, the amount of remaining glucose in the immature LJ group was significantly higher than that in the control group. These results suggest that immature LJE may inhibit the absorption of glucose into the small intestinal mucosa.

In addition, to analyze the mechanism of the inhibition of glucose absorption in the small intestine, the effect of immature LJE on glucose intake was estimated using Caco-2 cells and particularly by examining glucose transmission in monolayer Caco-2 cells. Caco-2 cells are derived from a colon carcinoma and represent a very common cell culture model for human enterocytes. Glucose was taken into Caco-2 cells and transported to a lower layer by glucose transporters in Caco-2 cells (Fig. 15.6).

To measure the level of D-[6-^{3}H] glucose intake in Caco-2 cells, tritium-labeled glucose and immature LJE were added to a culture medium. Phloridzin is an inhibitor of sodium-dependent glucose transporters. Glucose intake was significantly suppressed in phloridzin-treated Caco-2 cells, but not in those treated with immature LJE (Fig. 15.7).

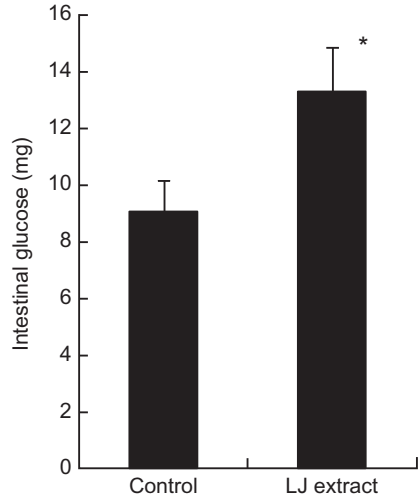

FIGURE 15.5 Effects of LJE on intestinal glucose absorption in mice. Data are expressed as the average ± SE ($n = 6$). $^*p < 0.05$ versus control.

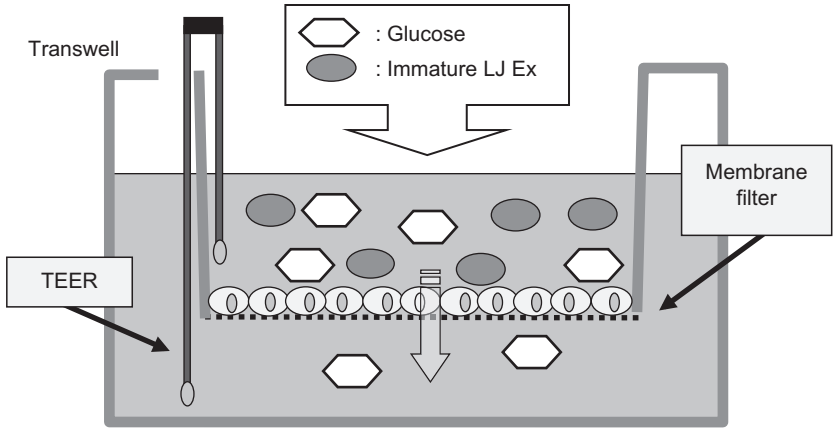

FIGURE 15.6 Scheme for the glucose transmission test of immature LJE in Caco-2 cells. Caco-2 cells were precultured for 2 weeks to cover the membrane filter as an experimental model for intestinal epithelia *in vitro*. Completion of the cell monolayer was detected by TEER measurement (Millicell-ERS). The transport of glucose from the upper cavity (apical site) to the lower cavity (basal site) through glucose transporters was evaluated by measuring both glucose concentrations for constant periods.

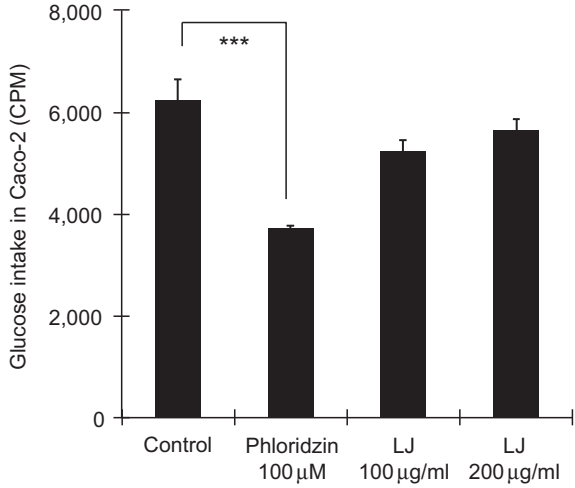

FIGURE 15.7 Effect of immature LJE on D-[6-^{3}H] glucose intake in Caco-2 cells. To measure the amount of glucose intake in Caco-2 cells, tritium-labeled glucose and immature LJE were added to the culture medium. Phloridzin inhibits sodium-dependent glucose transporters. Data are expressed as the average $\pm$ SE ($n = 4$). $^{***}p < 0.005$ versus control.

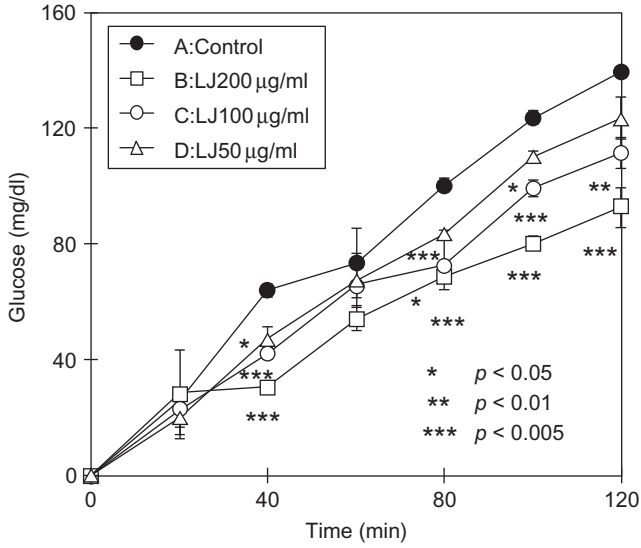

FIGURE 15.8 Effects of immature LJE on glucose transmission in Caco-2 cells. To measure the amount of glucose throughout the monolayer of Caco-2 cells, the amounts of glucose in the lower layer of the transwell were measured with or without immature LJE. Data are expressed as the average ± SE ($n = 4$). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.005$ versus control.

On the other hand, LJ suppressed glucose transmission from the upper layer to the lower layer in a concentrate-dependent manner, as shown in Fig. 15.8.

Caco-2 cells express sodium-dependent transporter 1 (SGLT1) in microvillus membrane and glucose transporter 2 (GLUT2) in the whole cell. This transporter operates via the glucose concentration in the small intestine. Mainly, SGLT1 or GLUT2 transports glucose from the gut lumen to cells and GLUT2 transports glucose from the apical side to the basolateral side. These results suggest that immature LJE did not affect glucose intake in Caco-2 cells but significantly suppressed the transmission of glucose in monolayer membranes by inhibiting GLUT2.

The results of the oral carbohydrate tolerance test and the long-term administration test suggest that immature LJE suppresses the postprandial blood glucose level. These results suggest that immature LJE can be used as a food for the prevention of diabetes. The active component in LJE remains to be elucidated.

IV. CONCLUSIONS

The popular edible seaweed LJ exhibited antiobesity and antidiabetic effects, as described above. In recent studies, the shaving process has been shown to alter the amount of active component that dissolves to cause physiological effects. The potential usefulness of *Laminaria* sp. as a marine medicinal food may be increased through the use of different processing methods and/or different growth stages. Such studies could provide new possibilities for the use of this seaweed. Therefore, these products of marine origin may be promising candidates for preventing obesity and diabetes and may continue to be one of the best marine medicinal foods for maintaining our good health in the future.

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