

# *Sargassum sagamianum* Extract Alleviates Postprandial Hyperglycemia in Diabetic Mice.

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**ABSTRACT:** In this study, we investigated the postprandial hypoglycemic effect of *Sargassum sagamianum* extract (SSE) in streptozotocin-induced diabetic mice. Freeze-dried *S. sagamianum* was extracted with 80% ethanol and concentrated. The inhibition of postprandial hyperglycemia was determined by the inhibitory activity against  $\alpha$ -glucosidase and  $\alpha$ -amylase as well as the measurement of postprandial blood glucose levels. SSE demonstrated a high inhibitory activity against  $\alpha$ -glucosidase and  $\alpha$ -amylase. The IC<sub>50</sub> value of SSE against  $\alpha$ -glucosidase and  $\alpha$ -amylase was 0.095 mg/mL and 0.199 mg/mL, respectively, and thus it was significantly more efficacious than the pharmaceutical acarbose (0.115 mg/mL and 0.229 mg/mL, respectively). The postprandial blood glucose levels in the SSE-administered group were significantly lower than those in the control group. Furthermore, the area under the curve significantly decreased following the administration of SSE. These results indicate that SSE can be used as an  $\alpha$ -glucosidase and  $\alpha$ -amylase inhibitor and can delay the absorption of dietary carbohydrates.

**Keywords:** *Sargassum sagamianum*,  $\alpha$ -glucosidase, postprandial hyperglycemia, diabetic mice

## INTRODUCTION

Type 2 diabetes is a major public health concern and accounts for 90% of the diabetes cases worldwide (1). Diabetes is also a progressive metabolic disorder and causes damage to several tissues, including kidney, nerves, retina, blood vessels, and other complications (2). A major characteristic of type 2 diabetes is fasting or postprandial hyperglycemia. Postprandial blood glucose levels could be a better marker of glycemic control than fasting blood glucose levels in patients with type 2 diabetes (3). Furthermore, an abnormal increase in postprandial blood glucose levels has been linked to the onset of type 2 insulin-independent diabetes mellitus and associated cardiovascular complications including hypertension (4). Thus, the control of postprandial hyperglycemia is important in the treatment of diabetes and the prevention of diabetic complications.

$\alpha$ -Glucosidase and  $\alpha$ -amylase play an important role in the control of blood glucose levels in the body. They are the key enzymes catalyzing the final step in the digestion of carbohydrates (4). The inhibition of both enzymes can slow down the digestion of carbohydrates, delay glucose absorption, and reduce blood glucose levels, resulting in a decrease in postprandial hyperglycemia (5). Some

drugs have been developed to improve postprandial hyperglycemia by inhibiting intestinal  $\alpha$ -glucosidase and  $\alpha$ -amylase activity (6). Antidiabetic drugs, such as acarbose, voglibose, and miglitol, are widely used in the treatment of type 2 diabetes (7). However, the pharmacological agents used for the treatment of type 2 diabetes appeared to have numerous limitations, and the chronic use of synthetic  $\alpha$ -glucosidase inhibitors has undesirable side effects, such as flatulence, diarrhea, and abdominal cramping. Thus, there is a need to develop natural  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitors with reduced side effects.

*Sargassum sagamianum*, an edible brown alga, can be harvested along the coastal area in Korea and Japan (8). *S. sagamianum* extract (SSE) exhibits anti-inflammatory (9) and antibacterial (10) effects. Furthermore, *S. sagamianum* has bioactive compounds such as plastoquinones, phlorotannins, and farnesylacetone derivatives, which exhibit cholinesterase inhibitory activity in Alzheimer's disease (1). However, the postprandial hypoglycemic effect of SSE has not yet been elucidated. Thus, this study was designed to investigate the inhibitory effect of SSE on  $\alpha$ -glucosidase and  $\alpha$ -amylase activities *in vitro* and its alleviating effect on postprandial hyperglycemia after a meal *in vivo*.

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## MATERIALS AND METHODS

### Materials

*S. sagamianum* was collected along the coast of Jeju Island, Korea. The samples were washed thrice with tap water to remove salt, epiphytes, and sand attached to the surface. Then, the samples were carefully rinsed with fresh water and freeze-dried. The dried sample was extracted with 10 volumes of 80% ethanol for 12 h thrice at room temperature. The filtrate was vacuum-evaporated to obtain the extract. The SSE was thoroughly freeze-dried and stored in a deep freezer ( $-80^{\circ}\text{C}$ ).

### Inhibition assay for *in vitro* $\alpha$ -glucosidase activity

The  $\alpha$ -glucosidase inhibition assay was conducted by the chromogenic method described by Watanabe et al. (12) using a readily available yeast enzyme. In brief, yeast  $\alpha$ -glucosidase (0.7 units, Sigma, St. Louis, MO, USA) was dissolved in 100 mM phosphate buffer (pH 7.0) containing 2 g/L bovine serum albumin and 0.2 g/L  $\text{NaN}_3$  to form the enzyme solution. p-Nitrophenyl- $\alpha$ -D-glucopyranoside (5  $\mu\text{M}$ ) was dissolved in the same buffer (pH 7.0) to form the substrate solution. Next, 50  $\mu\text{L}$  of enzyme solution and 10  $\mu\text{L}$  of sample dissolved in dimethylsulfoxide (5 mg/mL) were mixed in a well of a microtiter plate, and the absorbance was measured at 405 nm with a microplate reader (zero time point). After incubation for 5 min, the substrate solution (50  $\mu\text{L}$ ) was added, and the mixture was incubated for another 5 min at room temperature. Then, the increase in absorbance from the zero time point was measured. The inhibitory activity at varying concentrations of SSE was expressed as 100 minus the absorbance change of test compounds relative to the absorbance change of the control (%), where the test solution was replaced by the carrier solvent. The measurements were performed in triplicate, and the  $\text{IC}_{50}$  value (the concentration of SSE that results in 50% inhibition of maximal activity) was determined.

### Inhibition assay for *in vitro* $\alpha$ -amylase activity

The  $\alpha$ -amylase inhibition assay or the  $\alpha$ -glucosidase inhibition assay was conducted as previously described (13), except that porcine pancreatic amylase (100 units, Sigma) and p-nitrophenyl- $\alpha$ -D-maltopentoglycoside were used as the enzyme and substrate, respectively.

### Experimental animals

Four-week-old male mice (ICR, Orient Bio Inc., Seongnam, Korea) were used. All animals were housed individually in a light (12-h on/off) and temperature-controlled room with *ad libitum* access to pelleted food and water. After a 2-week adjustment period, diabetes was induced as described in the next subsection. All procedures were approved by the animal ethics committee of

our university (PNU-2016-1273).

### Induction of diabetes

To induce diabetes, mice were fasted for 18 h and intraperitoneally injected with 60 mg/kg streptozotocin (STZ) prepared in 0.1 M sodium citrate buffer (pH 4.5). One week after injection of STZ, fasting blood glucose levels were periodically measured using a glucometer (Roche Diagnostics GmbH, Mannheim, Germany). Blood was obtained via tail bleed. Mice with fasting blood glucose level of 250 mg/dL or higher were included in the diabetic groups.

### Measurement of blood glucose levels

Normal mice and STZ-induced diabetic mice were fasted overnight (deprived of food for at least 12 h but allowed free access to water). After overnight fasting, normal and STZ-induced diabetic mice were randomly divided into 3 groups of 7 mice (a total of 6 groups) and treated as follows: 1) control, mice received oral administration of soluble starch [2 g/kg body weight (BW)] alone; 2) SSE, mice received oral administration of starch with SSE (300 mg/kg BW); 3) acarbose, mice received oral administration of starch with acarbose (100 mg/kg BW). The SSE and acarbose doses were determined based on previous research (13,14). Blood samples were withdrawn from the tail vein at 0 min, 30 min, 60 min, and 120 min after oral administration. Blood glucose was measured using a glucometer (Roche Diagnostics GmbH). The area under the curve (AUC) for the glucose response was calculated using the trapezoidal rule (15).

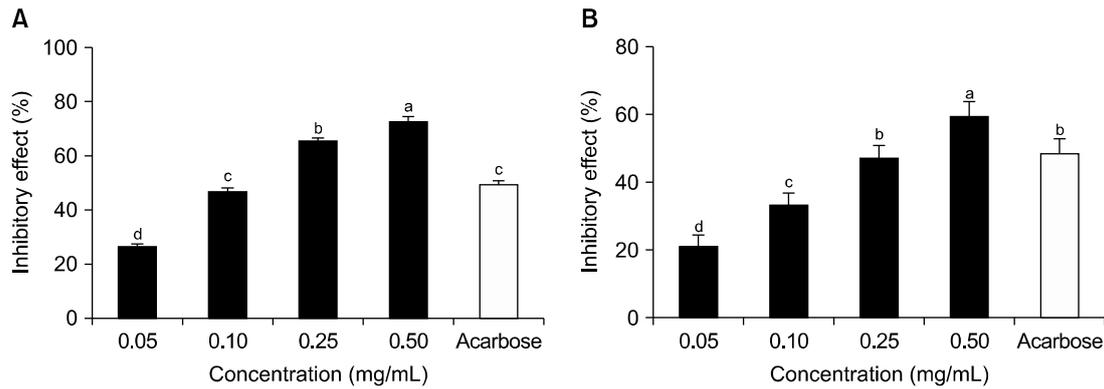
### Data and statistical analysis

The data are presented as mean  $\pm$  standard deviation. The statistical analysis was performed using SAS software (SAS Institute, Inc., Cary, NC, USA). The values were evaluated by one-way analysis of variance, followed by post-hoc Duncan's multiple range tests. The differences between the two groups were compared using *t*-tests ( $P < 0.05$ ).

## RESULTS AND DISCUSSION

### Inhibitory effect of SSE on $\alpha$ -glucosidase and $\alpha$ -amylase activities *in vitro*

The inhibitory effect of SSE on  $\alpha$ -glucosidase is shown in Fig. 1(A). SSE inhibited  $\alpha$ -glucosidase activity in a dose-dependent manner by 26.56%, 53.12%, 65.62%, and 73.43% at 0.05, 0.10, 0.25, and 0.50 mg/mL, respectively. Acarbose (an  $\alpha$ -glucosidase inhibitor), which is used as an oral hypoglycemic agent, inhibited the enzyme activity by 58.21% at 0.25 mg/mL. The inhibitory effect of SSE on  $\alpha$ -amylase increased in a dose-dependent manner



**Fig. 1.** Inhibitory activity of *Sargassum sagamianum* extract against  $\alpha$ -glucosidase (A) and  $\alpha$ -amylase (B). Each value is expressed as mean $\pm$ SD in triplicate experiments. Different letters (a-d) are significantly different at  $P < 0.05$ , analyzed by Duncan's multiple range test. Acarbose (0.25 mg/mL) was used as the positive control.

**Table 1.** IC<sub>50</sub> values of *Sargassum sagamianum* extract against  $\alpha$ -glucosidase and  $\alpha$ -amylase

Sample	IC <sub>50</sub> (mg/mL) <sup>1)</sup>	
	$\alpha$ -Glucosidase	$\alpha$ -Amylase
Acarbose	0.115 $\pm$ 0.007	0.229 $\pm$ 0.007
<i>Sargassum sagamianum</i> extract	0.095 $\pm$ 0.012*	0.199 $\pm$ 0.007*

Each value is expressed as mean $\pm$ SD in triplicate experiments. \* $P < 0.05$  compared with the control group.

<sup>1)</sup>IC<sub>50</sub> value is the concentration of the sample required for 50% inhibition.

[21.51%, 33.33%, 55.91%, and 59.25% at 0.05, 0.10, 0.25, and 0.50 mg/mL, respectively; Fig. 1(B)]. SSE also inhibited  $\alpha$ -amylase activity more effectively than acarbose. The IC<sub>50</sub> values of SSE against  $\alpha$ -glucosidase and  $\alpha$ -amylase were 0.095 and 0.199 mg/mL, respectively, which indicated a significantly stronger inhibitory effect than that of acarbose (Table 1).

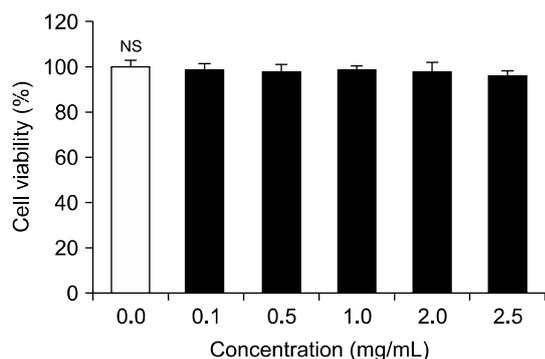
The treatment goal for diabetic patients is to maintain glycemic levels in fasting and postprandial states (14). The most effective diet or therapeutic approach to prevent and treat diabetes and its complications is to decrease the postprandial hyperglycemia by delaying the absorption of glucose in the small intestine (15). The inhibition of carbohydrate-hydrolyzing enzymes is one of the best methods for controlling postprandial hyperglycemia to delay glucose absorption. Pancreatic  $\alpha$ -amylase and intestinal  $\alpha$ -glucosidase are the hydrolyzing enzymes responsible for glucose generation through diet.  $\alpha$ -Amylase hydrolyzes  $\alpha$ -1,4-glycosidic bonds and splits up starch components, such as amylose and amylopectin, into smaller oligosaccharides and disaccharides, such as maltose (16). Similarly,  $\alpha$ -glucosidase is located on the brush-border surface membrane of intestinal cells.  $\alpha$ -Glucosidase catalyzes the hydrolysis of disaccharides and oligosaccharides present in the lumen of the intestine. Thus, the glucose generated by  $\alpha$ -glucosidase activity is readily available for intestinal absorption (17). The in-

hibition of its activity in the digestive path of humans is considered to be effective in the control of diabetes due to the decreased absorption of glucose decomposed from starch by these enzymes (18). In this study, SSE showed a significantly higher inhibitory effect than acarbose on  $\alpha$ -glucosidase and  $\alpha$ -amylase, which suggested that SSE could control diabetes by reducing postprandial hyperglycemia. Oral drugs exert an anti-hyperglycemic effect by ameliorating the major metabolic defects that cause hyperglycemia, or reducing the postprandial increase in glycemic levels by impeding carbohydrate digestion and absorption in the gut (19). Acarbose is an antidiabetic drug, which delays glucose absorption from the gastrointestinal tract, attenuating postprandial increase in blood glucose levels. However, it has side effects such as vomiting, abdominal fullness, pancreatitis, and possibly diarrhea (20). Thus, effective and nontoxic natural inhibitors of  $\alpha$ -glucosidase and  $\alpha$ -amylase have long been sought.

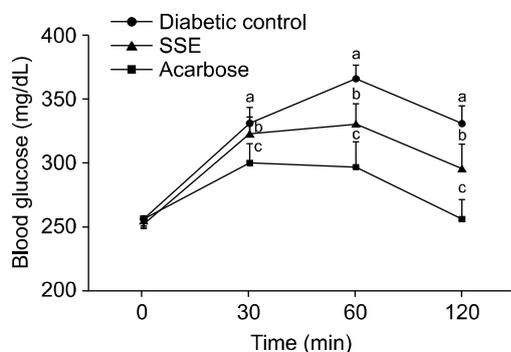
In this study, we investigated the inhibitory effect of SSE on  $\alpha$ -glucosidase and  $\alpha$ -amylase to elucidate the potential of SSE as a natural agent in reducing postprandial hyperglycemia. SSE exhibited a high inhibitory activity against  $\alpha$ -glucosidase and  $\alpha$ -amylase without any cytotoxicity (Fig. 2). It contains various types of polyphenols, such as plastoquinones, phlorotannins, fucoxanthin, and sargachromanol. Hydrogen bonds are formed between the hydroxyl group in polyphenols and the carboxylate group in Asp197 and Glu233 at the active site of the enzyme (21). Thus, polyphenolic compounds containing SSE may bind to the active site of the carbohydrate digestive enzymes, resulting in the inhibition of the enzymes activity.

#### Effect of SSE on postprandial blood glucose levels *in vivo*

The effect of SSE on postprandial blood glucose levels was investigated in STZ-induced diabetic and normal mice. SSE (300 mg/kg) and acarbose (100 mg/kg) were co-administered orally with starch (2 g/kg). In the diabetic mice, postprandial blood glucose levels in the SSE

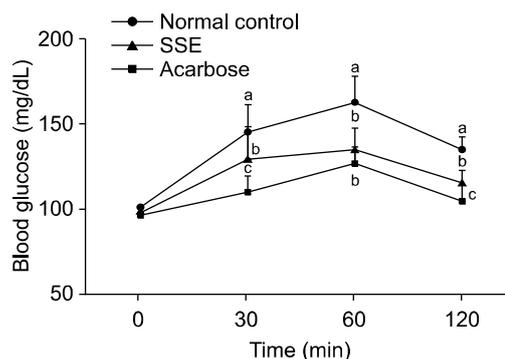


**Fig. 2.** Cytotoxic effect of *Sargassum sagamianum* extract (SSE) on 3T3-L1 cells. 3T3-L1 cells were treated with various concentrations (0.1, 0.5, 1.0, 2.0, and 2.5 mg/mL) of SSE for 20 h, and cell viability was measured via MTT assay. Each value is expressed as mean $\pm$ SD in triplicate experiments. NS: non-significant.



**Fig. 3.** Blood glucose levels after administration of *Sargassum sagamianum* extract (SSE) in streptozotocin-induced diabetic mice. Control (distilled water), SSE (300 mg/kg), and acarbose (100 mg/kg) were co-administered orally with starch (2 g/kg). Each value is expressed as mean $\pm$ SD of seven mice (n=21). Different letters (a-c) are significantly different at  $P<0.05$ , analyzed by Duncan's multiple range test.

administered group were significantly lower than those in the control group (Fig. 3). Blood glucose levels of the control group increased to 362 mg/dL at 60 min after the meal and decreased thereafter. However, postprandial blood glucose levels were significantly alleviated ( $P<0.05$ ) when diabetic mice were fed SSE (321.2 mg/dL, 339.6 mg/dL, and 295.6 mg/dL at 30 min, 60 min, and 120 min, respectively). In normal mice, SSE also significantly alleviated ( $P<0.05$ ) postprandial hyperglycemia caused by starch. The peak of postprandial blood glucose levels significantly decreased when SSE with starch was orally administered to normal mice (Fig. 4). In the diabetic mice, the AUC for the glucose response was significantly lower in the SSE-administration group ( $624.26\pm 75.12$  mg $\cdot$ h/dL) than in the control group ( $662.31\pm 40.92$  mg $\cdot$ h/dL) (Table 2). The AUCs in normal mice showed the same pattern as that in diabetic mice, supporting the anti-postprandial hyperglycemic effect of SSE. The medicine that lowers the peak level of postprandial blood glucose decreases the AUC for the blood glucose response



**Fig. 4.** Blood glucose levels after administration of *Sargassum sagamianum* extract (SSE) in normal mice. Control (distilled water), SSE (300 mg/kg), and acarbose (100 mg/kg) were co-administered orally with starch (2 g/kg). Each value is expressed as mean $\pm$ SD of seven mice (n=21). Different letters (a-c) are significantly different at  $P<0.05$ , analyzed by Duncan's multiple range test.

**Table 2.** Areas under the curve (AUC) for postprandial glucose response in normal and streptozotocin-induced diabetic mice

Group	AUC (mg $\cdot$ h/dL)	
	Normal mice	Diabetic mice
Control	247.50 $\pm$ 20.45 <sup>a</sup>	662.31 $\pm$ 40.92 <sup>a</sup>
SSE	207.75 $\pm$ 24.49 <sup>b</sup>	624.26 $\pm$ 75.12 <sup>b</sup>
Acarbose	187.90 $\pm$ 23.74 <sup>c</sup>	561.31 $\pm$ 47.32 <sup>c</sup>

*Sargassum sagamianum* extract (SSE, 300 mg/kg), acarbose (100 mg/kg), and control (distilled water) were co-administered orally with starch (2 g/kg). Each value is expressed as mean $\pm$ SD of seven mice (n=42). Different letters (a-c) are significantly different at  $P<0.05$ , analyzed by Duncan's multiple range test.

(22). This study showed that SSE significantly decreased both the postprandial blood glucose at the peak time point and the AUC. Controlling postprandial hyperglycemia is important to manage blood glucose levels, which is the major target in diabetic therapy (23). Furthermore, postprandial hyperglycemia is an independent risk factor for cardiovascular complications, which is the major cause of premature death among type 2 diabetic patients (24,25).

We investigated the antipostprandial hyperglycemic effect of SSE in STZ-induced diabetic and normal mice after the consumption of starch. SSE significantly suppressed the increase in postprandial blood glucose levels in STZ-induced diabetic and normal mice. These results indicate that SSE may delay the absorption of dietary carbohydrates.

Type 2 diabetic patients have postprandial hyperglycemia, which over a long duration induces metabolic disorders and diabetic complications. Thus, the regulation of postprandial hyperglycemia is important in the treatment of diabetes and prevention of its complications (26). Many synthetic compounds, such as acarbose and voglibose, have been used in the treatment of diabetes (27).

However, the inhibition of  $\alpha$ -glucosidase and  $\alpha$ -amylase by such inhibitors has not been satisfactory, and prolonged use causes harmful side effects, including diarrhea, abdominal pain, and flatulence. Therefore, the search for natural extracts and inhibitors of enzymes must continue (28). The results of our study suggest that SSE may alleviate postprandial hyperglycemia by inhibiting  $\alpha$ -amylase and  $\alpha$ -glucosidase.

In conclusion, SSE inhibited  $\alpha$ -glucosidase and  $\alpha$ -amylase activities and delayed the digestion and absorption of dietary starch, thereby reducing postprandial hyperglycemia.

Thus, we suggest that SSE can be developed as a functional food. However, further studies are warranted to identify the active compounds with antidiabetic effects.

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## AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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