

# Alleviating Effects of *Baechu Kimchi* Added *Ecklonia cava* on Postprandial Hyperglycemia in Diabetic Mice

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**ABSTRACT:** In this study, we investigated the inhibitory effects of *Baechu kimchi* added *Ecklonia cava* on the activities of  $\alpha$ -glucosidase and  $\alpha$ -amylase and its alleviating effect on the postprandial hyperglycemia in STZ-induced diabetic mice. *Baechu kimchi* added *Ecklonia cava* (BKE, 15%) was fermented at 5°C for 28 days. Optimum ripened BKE was used in this study as it showed the strongest inhibitory activities on  $\alpha$ -glucosidase and  $\alpha$ -amylase by fermentation time among the BKEs in our previous study. The BKE was extracted with 80% methanol and the extract solution was concentrated, and then used in this study. The BKE extract showed higher inhibitory activities than *Baechu kimchi* extract against  $\alpha$ -glucosidase and  $\alpha$ -amylase. The IC<sub>50</sub> values of the BKE extract against  $\alpha$ -glucosidase and  $\alpha$ -amylase were 0.58 and 0.35 mg/mL, respectively; BKE exhibited a lower  $\alpha$ -glucosidase inhibitory activity but a higher  $\alpha$ -amylase inhibitory activity than those of acarbose. The BKE extract alleviated postprandial hyperglycemia caused by starch loading in normal and streptozotocin-induced diabetic mice. Furthermore, the BKE extract significantly lowered the incremental area under the curve in both normal and diabetic mice ( $P < 0.05$ ). These results indicated that the BKE extract may delay carbohydrate digestion and thus glucose absorption.

**Keywords:** *Baechu kimchi*, *Ecklonia cava*,  $\alpha$ -glucosidase,  $\alpha$ -amylase, postprandial hyperglycemia

## INTRODUCTION

Diabetes mellitus has become an abiding interest of all modern societies with recent increases in the prevalence of risk factors such as abdominal obesity, dislipidemia and hypertension. The prevalence of diabetic patients worldwide has dramatically increased due to modern lifestyle and an increase of consumption in high carbohydrate diets (1). Diabetes sufferers have high blood glucose levels due to either not enough insulin production or cells of the liver, muscles and fat tissue do not respond to insulin in a normal way (2). One important approach for suppressing postprandial hyperglycemia is to reduce or slow dietary carbohydrate digestion and absorption. Starch digestion primarily occurs in the small intestine through the action of pancreatic  $\alpha$ -amylase, yielding both linear maltose and branched isomaltose oligosaccharides, which are further hydrolyzed by intestinal  $\alpha$ -glucosidase (3). By inhibiting the enzymes involved in carbohydrate digestion, postprandial hyperglycemia can be significantly delayed, which may have beneficial effects on insulin resistance and glycemic in-

dex control in diabetic patients (4). Current pharmacotherapeutics insufficiently reverse hyperglycemia, have limited tolerability and induced side effects (5). Hence, much effort has been extended in search of effective  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitors from natural sources in order to develop physiologically functional foods and introduce natural medicines (6,7).

*Ecklonia cava*, a marine brown alga, is widely distributed in the subtidal zone off the southern coasts of Korea and Japan and is plentifully produced, about 30,000 tons per year, for commercial purpose on Jeju Island of Korea. *E. cava* is utilized as food ingredients, animal feed, fertilizers as well as raw materials to produce fucoidan or phlorotannin. According to numerous investigations, *Ecklonia cava* exhibits various bioactivities, such as anti-allergic, antiviral, and anti-diabetic (8-10).

*Baechu kimchi* is a salt fermented cabbage widely consumed in traditional Korean foods. Various unique microorganisms and bioactive components present in *Baechu kimchi* show antioxidant ability (11), an elevated immune response (12) and anti-cancer (13) and anti-diabetic effects (14). A previous study indicated that the

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supplement of *Baechu kimchi* improved fasting blood glucose and insulin resistance in a high-fat diet-fed rat model (14). However, a research of *Baechu kimchi* about the inhibitory effect of  $\alpha$ -glucosidase and postprandial hyperglycemia has not been carried out yet. Thus, this study was conducted to investigate the inhibitory effects of *Baechu kimchi* added *Ecklonia cava* on the activities of  $\alpha$ -glucosidase and  $\alpha$ -amylase and its alleviating effect on postprandial hyperglycemia in STZ-induced diabetic mice.

## MATERIALS AND METHODS

### Materials

*Ecklonia cava* was collected along the coast of Jeju Island, Korea. The samples were washed three times with tap water to remove the salt, epiphytes, and sand attached to the surface, then carefully rinsed with fresh water. *Ecklonia cava* was boiled with 0.3% citric acid in water for 10 min for softening. *Baechu* (Korean cabbage) was divided in four pieces and then 3% salt (w/w) compared to *Baechu* was evenly sprinkled over the cabbage. Spliced *Baechu* was pickled in 10% salty water until reaching salinity at  $1.8 \pm 0.1$ . After the salted cabbages were washed twice under running water, it was naturally dehydrated for 2 h. *Baechu kimchi* was prepared by mixing salted cabbage with spice ingredients and 15% of *Ecklonia cava* (Table 1). *Baechu kimchi* added *Ecklonia cava* (BKE) was fermented at 5°C for 28 days. Each sample was made with fresh, optimum ripened and over ripened BKE. Optimum ripened BKE (pH 4.28, acidity 0.71), which had been fermented for 20 days at 5°C, was used in this study since optimum ripened BKE had the strongest inhibitory activities against  $\alpha$ -glucosidase and  $\alpha$ -amylase by fermentation time among the BKEs in our previous study. The BKE was extracted with 80% methanol and the extracts solution was concentrated. Then, dried BKE extract was stored in a deep freezer ( $-80^{\circ}\text{C}$ ).

**Table 1.** Recipes of *Baechu kimchi* added *Ecklonia cava* and *Baechu kimchi* used in this study

Ingredients	<i>Baechu kimchi</i> added <i>Ecklonia cava</i> (%)	<i>Baechu kimchi</i> (%)
Korean cabbage	85.00	97.75
<i>Ecklonia cava</i>	12.75	-
Green onion	2.30	2.30
Garlic	2.50	2.50
Ginger	0.50	0.50
Red pepper powder	2.60	2.60
Fermented shrimp juice	1.70	1.70
Sand eel fermented juice	1.30	1.30
Glutinous rice paste	3.60	3.60
Sugar	0.50	0.50
Total	100.00	100.00

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

The  $\alpha$ -glucosidase inhibitory assay was done by the chromogenic method developed by Watanabe et al. using a readily available yeast enzyme (15). Briefly, yeast  $\alpha$ -glucosidase (0.7 U, 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  $\text{NaN}_3$  and used as an enzyme solution. 5 mM p-nitrophenyl- $\alpha$ -D-glucopyranoside in the same buffer (pH 7.0) was used as a substrate solution. The 50  $\mu\text{L}$  of enzyme solution and 10  $\mu\text{L}$  of sample dissolved in dimethylsulfoxide at a 5 mg/mL concentration were mixed in a well, and absorbance at 405 nm was measured using a microplate reader (Medel 680, BioRad, Hercules, CA, USA). After incubation for 5 min, substrate solution (50  $\mu\text{L}$ ) was added and incubated for another 5 min at room temperature. The increase in absorbance from zero time was measured. Inhibitory activity was expressed as 100 minus relative absorbance difference (%) of test compounds to absorbance change of the control, where carrier solvent replaced the test solution. The measurements were performed in triplicate and  $\text{IC}_{50}$  value, i.e., the concentration of the extracts that results in 50% inhibition of maximal activity, was determined.

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

The  $\alpha$ -amylase inhibitory activity was assayed in the same way (15) as described for the  $\alpha$ -glucosidase inhibitory assay above, except that porcine pancreatic amylase (100 U, Sigma) and blocked p-nitrophenyl- $\alpha$ -D-maltopentoglycoside (Sigma) were used as enzyme and substrate, respectively.

### Experimental animals

Four-week old male mice (ICR, Orient Bio Inc., Seoul, Korea) were kept under a 12 h light/12 h dark cycle with room temperature controlled. The animals were maintained with pelleted food, while tap water was *ad libitum*. After an adjustment period of 2 weeks, diabetes was induced by intraperitoneal injection of STZ (60 mg/kg) freshly dissolved in citrate buffer (0.1 M, pH 4.5) in the fasted (18 h) animals. After seven days, tail bleeds were performed and animals with a blood glucose concentration above 300 mg/dL were considered to be diabetic.

### Measurement of blood glucose level

Both normal mice and STZ-induced diabetic mice fasted overnight were randomly divided into four groups. Fasted animals were deprived of food for at least 12 h but allowed free access to water. After overnight fasting, the mice were administered orally either soluble starch (2 g/kg body weight) alone (control) or starch with BKE extract (300 mg/kg body weight). Blood samples were taken from the tail vein at 0, 30, 60, and 120 min. Blood

glucose was measured using a glucometer (Roche Diagnostics GmbH, Mannheim, Germany). Areas under the curve (AUC) were calculated using the trapezoidal rule (16). All procedures were approved by the animal ethics committee of our university (PNU-2012-0039).

### Data statistical analysis

The data were represented as mean±SD. The statistical analysis was performed using SAS 9.1 software (SAS Institute Inc, Cary, NC, USA). The Student's *t*-test was used for comparisons between control and sample groups. The values were evaluated by one-way analysis of variance (ANOVA) followed by post-hoc Duncan's multiple range tests.

## RESULTS AND DISCUSSION

### Inhibitory effect of BKE extract on $\alpha$ -glucosidase and $\alpha$ -amylase *in vitro*

The inhibitory effect of *Baechu kimchi* added *Ecklonia cava* (BKE) extract against  $\alpha$ -glucosidase is shown in Fig. 1. BKE extract inhibited  $\alpha$ -glucosidase activity in a dose dependent manner (35.43, 41.23, 48.71 and 56.92% at 0.1, 0.25, 0.5, and 1.0 mg/mL concentrations, respectively). Moreover,  $\alpha$ -glucosidase inhibitory activity of BKE extract was higher than that of *Baechu kimchi* extract. Acarbose, an  $\alpha$ -glucosidase inhibitor, used as an oral hypoglycemic agent, inhibited the enzyme activity by 62.03% at a concentration of 0.5 mg/mL. The inhibitory effect of BKE extract against  $\alpha$ -amylase is shown in Fig. 2. The BKE extract inhibited  $\alpha$ -amylase by 35.24, 47.81, 53.13 and 58.96% at concentrations of 0.1, 0.25, 0.5, and 1.0 mg/mL, respectively. The BKE extract inhibited the  $\alpha$ -amylase more effectively than *Baechu kimchi* extract. The  $\alpha$ -amylase inhibitory activity of BKE extract at the

concentration of 0.5 mg/mL was similar to that of acarbose at the same concentration. The IC<sub>50</sub> values of the BKE extract against  $\alpha$ -glucosidase and  $\alpha$ -amylase were 0.58 and 0.35 mg/mL, respectively, which were stronger than those of *Baechu kimchi* extract. Further, the IC<sub>50</sub> values of the BKE extract showed a lower  $\alpha$ -glucosidase inhibitory activity but a higher  $\alpha$ -amylase inhibitory activity compared to acarbose (Table 2).

Starch digestion primarily occurs in the small intestine through the action of pancreatic  $\alpha$ -amylase, yielding both linear maltose and branched isomaltose oligosaccharides, which are further hydrolyzed by intestinal  $\alpha$ -glucosidases to release absorbable monosaccharides. The  $\alpha$ -glucosidase inhibitors impede carbohydrate hydrolysis by inhibiting glucosidase enzymes in the brush border of the small intestine. The low speed of digestion and absorption of carbohydrates reduces the postprandial rise in plasma glucose (17). Thus the  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitors prevent high glucose concentration in the blood after a meal (3). Controlling both fasting and postprandial hyperglycemia are the major targets of diabetic therapy (18). Previously known, postprandial hyperglycemia might have a stronger correlation with car-

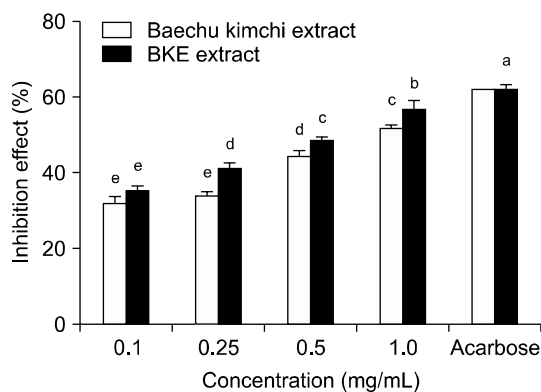
**Table 2.** IC<sub>50</sub> values for the inhibitory effects of BKE extract on  $\alpha$ -glucosidase and  $\alpha$ -amylase

Sample	IC <sub>50</sub> (mg/mL) <sup>1)</sup>	
	$\alpha$ -Glucosidase	$\alpha$ -Amylase
BKE extract	0.58±0.01 <sup>b</sup>	0.35±0.01 <sup>c</sup>
<i>Baechu kimchi</i> extract	0.88±0.02 <sup>a</sup>	0.80±0.02 <sup>a</sup>
Acarbose	0.34±0.02 <sup>c</sup>	0.45±0.04 <sup>b</sup>

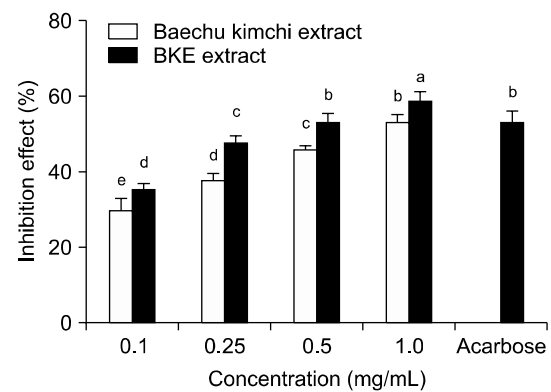
<sup>1)</sup>IC<sub>50</sub> value is the concentration of sample required for 50% inhibition. Each value is expressed as mean±SD (n=3).

<sup>a-c</sup>Values with different alphabets in a column are significantly different at *P*<0.05 as analyzed by Duncan's multiple range test.

BKE extract: *Baechu kimchi* added *Ecklonia cava* extract.



**Fig. 1.** Inhibitory activity of BKE extract on  $\alpha$ -glucosidase. Each value is expressed as mean±SD in triplicate experiments. <sup>a-e</sup>Values with different alphabets are significantly different at *P*<0.05 as analyzed by Duncan's multiple range test. The concentration of acarbose used as positive control was 0.5 mg/mL. BKE extract: *Baechu kimchi* added *Ecklonia cava* extract.



**Fig. 2.** Inhibitory activity of BKE extract on  $\alpha$ -amylase. Each value is expressed as mean±SD in triplicate experiments. <sup>a-e</sup>Values with different alphabets are significantly different at *P*<0.05 as analyzed by Duncan's multiple range test. The concentration of acarbose used as positive control was 0.5 mg/mL. BKE extract: *Baechu kimchi* added *Ecklonia cava* extract.

diovascular morbidity and mortality than fasting hyperglycemia (19). Hence, the decrease in postprandial hyperglycemia by retarding the absorption of glucose through the inhibition of carbohydrate-hydrolyzing enzymes, such as  $\alpha$ -amylase and  $\alpha$ -glucosidase, would play a key role in the control of diabetes (20,21).

*Baechu kimchi* contains several ingredients in addition to Chinese cabbage, such as onion, ginger, garlic, and red pepper, which have proven hypoglycemic (22,23), insulinotropic (24) and antidiabetic effects (25,26). Our data showed that BKE extract had higher inhibitory activities than *Baechu kimchi* extract on  $\alpha$ -glucosidase and  $\alpha$ -amylase, suggesting that addition of *E. cava* in *Baechu kimchi* may delay the digestion and absorption of carbohydrates.

### Effect of BKE extract on blood glucose level *in vivo*

The alleviating effect of BKE extract on hyperglycemia after a meal was investigated in STZ-induced diabetic and normal mice. Postprandial blood glucose levels in the BKE extract-administered diabetic mice were significantly lower than those of the mice in the control group (Fig. 3). The blood glucose levels of diabetic mice in the control group were 430.5, 465.0 and 464.0 mg/dL at 30, 60 and 120 min, respectively; however, the increase in postprandial blood glucose levels was significantly reduced ( $P<0.05$ ) in diabetic mice administered BKE extract (402.4, 405.0 and 377.0 mg/dL at the same respective time points), which were lower than those of the *Baechu kimchi* extract. The postprandial blood glucose level was also significantly decreased when normal mice were orally administered starch with BKE extract (Fig. 4). The area under the two-hour blood glucose response curve (AUC) of the BKE extract-ad-

ministered group ( $790.08\pm69.22$  mg·h/dL) was significantly lower ( $P<0.05$ ) than the control group ( $883.50\pm71.08$  mg·h/dL) in the diabetic mice (Table 3).

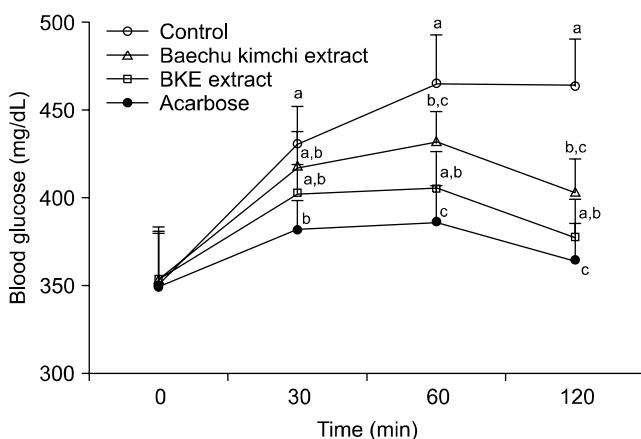
Postprandial hyperglycemia is the earliest metabolic abnormality to take place in type 2 diabetes (27). The treatment goal for patients with type 2 diabetes is generally agreed to maintain near-normal levels of glycemic control, both in the fasting and postprandial states (28). Fig. 3 and 4 suggest that the hypoglycemic effect of BKE extract was higher than that of *Baechu kimchi* extract on starch loading. The increase in postprandial blood glucose level was significantly suppressed by BKE extract administration in both STZ-induced diabetic and normal mice. These results indicate that BKE extract may delay the absorption of dietary carbohydrates consumed, resulting in suppressing an increase in postprandial blood glucose levels. Management of diabetes is not only related to the increased release of insulin and its action for

**Table 3.** Area under the curve (AUC) of postprandial glucose responses of normal and streptozotocin-induced diabetic mice

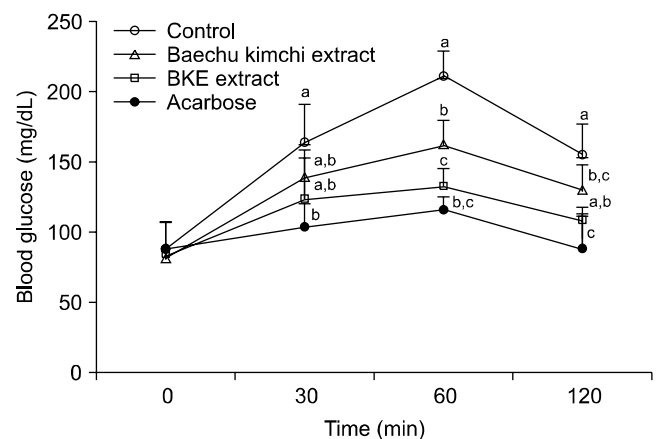
Group <sup>1)</sup>	AUC (mg·h/dL)	
	Normal mice	Diabetic mice
BKE extract	236.01±62.33 <sup>b</sup>	790.08±69.22 <sup>ab</sup>
<i>Baechu kimchi</i> extract	275.75±31.75 <sup>b</sup>	836.65±58.99 <sup>ab</sup>
Acarbose	204.68±33.35 <sup>b</sup>	749.10±32.76 <sup>b</sup>
Control	339.98±4.23 <sup>a</sup>	883.50±71.08 <sup>a</sup>

<sup>1)</sup> *Baechu kimchi* added *Ecklonia cava* extract (BKE extract, 300 mg/kg), *Baechu kimchi* extract (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±SD of 7 mice (n=42).

<sup>a-b</sup> Values with different alphabets in a column are significantly different at  $P<0.05$  as analyzed by Duncan's multiple range test.



**Fig. 3.** Blood glucose levels after the administration of BKE extract in streptozotocin-induced diabetic mice. Control (distilled water), BKE extract (300 mg/kg), *Baechu kimchi* (300 mg/kg) and acarbose (100 mg/kg) were co-administered orally with starch (2 g/kg). Each value is expressed as mean±SD of seven mice (n=21). <sup>a-c</sup> Values with different alphabets are significantly different at  $P<0.05$  as analyzed by Duncan's multiple range test. BKE extract: *Baechu kimchi* added *Ecklonia cava* extract.



**Fig. 4.** Blood glucose levels after the administration of BKE extract in normal mice. Control (distilled water), BKE extract (300 mg/kg), *Baechu kimchi* (300 mg/kg) and acarbose (100 mg/kg) were co-administered orally with starch (2 g/kg). Each value is expressed as mean±SD of seven mice (n=21). <sup>a-c</sup> Values with different alphabets are significantly different at  $P<0.05$  as analyzed by Duncan's multiple range test. BKE extract: *Baechu kimchi* added *Ecklonia cava* extract.

glycemic control, but also important in controlling the glycemic index and postprandial hyperglycemia (29). Postprandial hyperglycemia is involved in a variety of metabolic disorders and other diseases such as cardiac dysfunction (30) and cancer (31). Since  $\alpha$ -glucosidase inhibitors delay the rate of transition from disaccharide to monosaccharide, the postprandial blood glucose is maintained at a lower level (32). Acarbose, an anti-diabetic drug used to treat type 2 diabetes by inhibiting the  $\alpha$ -glucosidase in the brush border of the small intestine, has demonstrated that long-term treatment decreases the risk of diabetes, hypertension, and cardiovascular diseases (33). Interestingly, acarbose treatment helps to reduce progression of intima-media thickness of the carotid arteries in subjects with impaired glucose tolerance, a state of high risk for diabetes and atherosclerosis (34). Despite the multiple benefits of acarbose, this drug causes gastrointestinal problems such as sour stomach, belching, nausea, vomiting, indigestion, and diarrhea (35). Therefore, a necessary need exists to discover and develop safe and more effective antidiabetic agents. Lately, alternative therapies, including the functional food for treating diabetes, is showing a growing interest (36).

In conclusion, the present study demonstrates that BKE extract alleviated postprandial hyperglycemia by inhibiting the activities of  $\alpha$ -glucosidase and  $\alpha$ -amylase in STZ-induced diabetic mice. Thus, BKE extract may be helpful in improving blood glucose level after a meal.

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## AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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