

Antihypertensive effect of an enzymatic hydrolysate from *Styela clava* flesh tissue in type 2 diabetic patients with hypertension

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BACKGROUND/OBJECTIVES: In this randomized, placebo-controlled, double-blind study, we evaluated the antihypertensive effects of enzymatic hydrolysate from *Styela clava* flesh tissue in patients with type 2 diabetes mellitus (T2DM) and hypertension.

SUBJECTS/METHODS: *S. clava* flesh tissue hydrolysate (SFTH) (n = 34) and placebo (n = 22) were randomly allocated to the study subjects. Each subject ingested two test capsules (500 mg) containing powdered SFTH (SFTH group) or placebo capsules (placebo group) during four weeks.

RESULTS: In the SFTH group, systolic and diastolic blood pressure decreased significantly 4 weeks after ingestion by 9.9 mmHg ($P < 0.01$) and 7.8 mmHg ($P < 0.01$), respectively. In addition, the SFTH group exhibited a significant decrease in hemoglobin A_{1c} with a tendency toward improvement in homeostasis model assessment of insulin resistance, triglyceride, apolipoprotein B and plasma insulin levels after 4 weeks. No adverse effects were observed in other indexes, including biochemical and hematological parameters in both groups.

CONCLUSION: The results of our study suggested that SFTH exerts a regulatory, antihypertensive effect in patients with T2DM and hypertension.

Nutrition Research and Practice 2017;11(5):396-401; <https://doi.org/10.4162/nrp.2017.11.5.396>; pISSN 1976-1457 eISSN 2005-6168

Keywords: Aquatic organisms, protein hydrolysates, clinical trial, antihypertensive agents

INTRODUCTION

Diabetes and metabolic syndrome have become major problems, and these are both related to cardiovascular diseases (CVDs) and other risk factors, including hypertension, hypertriglyceridemia and insulin resistance [1]. According to the Adult Treatment Panel III the National Cholesterol Education Program (NCEP-ATTP-III) guidelines, metabolic syndrome is identifying the presence of three or more of the following defining risk factors: abdominal obesity (waist circumference $\geq 102/88$ cm in males/females), triglycerides (≥ 150 mg/dL under fasting conditions or fibrate or nicotinic acid therapy), fasting glucose (≥ 100 mg/dL or glucose-lowering treatment or previously diagnosed diabetes mellitus), systolic/diastolic blood pressure ($\geq 130/85$ mmHg or antihypertensive treatment) and fasting high density lipoprotein (HDL) cholesterol ($< 40/50$ mg/dL in males/females) [2].

Artery structure is changed by increased blood pressure (BP). Risks of CVDs increase, not only in patients with high blood

pressure, but also in those with normal blood pressure [3]. Among the major factors related to high blood pressure, angiotensin I-converting enzyme (ACE) is associated with elevation of blood pressure in the renin angiotensin system (RAS) and kallikrein kinin system (KKS) [4,5]. In the RAS, ACE produces angiotensin II with vasoconstrictive activity, while in the KKS, ACE inactivates bradykinin with the ability to induce vascular relaxation [4,6,7]. Therefore, effective inhibition of ACE is one of the key actions required for the reduction of high blood pressure. However, the currently employed synthetic anti-ACE agents reportedly have adverse effects, such as hyperkalemia, headache, dizziness, fatigue and nausea [8,9]. Due to these adverse side effects, identifying a safe anti-ACE agent from food resources has been the subject of alternative therapies for hypertension. Possible mechanisms for the reduction of blood pressure involve promoting vasorelaxation [10]. Production of nitric oxide (NO) by endothelial nitric oxide synthesis (eNOS) in the endothelium leads to vasorelaxant effect in hypertension [11].

This research was supported by the 2016 scientific promotion program funded by Jeju National University, as well as by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Korea (HI14C1135).

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Received: May 2, 2017, Revised: May 14, 2017, Accepted: July 20, 2017

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Our previous studies have proposed that the *S. clava* flesh tissue can be considered a potential antihypertensive agent. For example, the enzymatic hydrolysate from *S. clava* flesh tissue inhibited ACE activity [11]. Moreover, the enzymatic hydrolysate exerted a vasorelaxation effect in response to NO produced by eNOS in the rat thoracic aorta. Further, a previous *in vivo* experiment revealed that oral administration of the enzymatic hydrolysate induced a reduction of BP in an *in vivo* model of hypertension [10]. Despite the aforementioned preclinical data, there is a lack of data regarding human clinical trials of enzymatic hydrolysate from *S. clava* flesh tissue. Thus, we conducted a double-blinded, randomized, and placebo-controlled study to evaluate the antihypertensive effects of the enzymatic hydrolysate from *S. clava* flesh tissue in patients with Type 2 diabetes mellitus (T2DM) and hypertension.

SUBJECTS AND METHODS

Materials

Styela clava flesh tissue was obtained from Miduduk Corporated Association (Changwon, Gyeongsangnam-do, Korea). Protamex was purchased from Novozyme Co. (Bagasvaerd, Hovedstaden, Denmark). All other chemicals and reagents were of analytical grade.

Preparation of *S. clava* flesh tissue hydrolysate (SFTH)

S. clava flesh tissue powder was hydrolyzed with Protamex in buffer solution for 24 h according to our previous method [11]. The enzyme was then subjected to inactivation at 100°C for 10 min, after which the solution was filtered. Following removal of the insoluble materials by centrifugation at 3,000 × g for 20 min, the soluble hydrolysate in the supernatant was lyophilized to yield *S. clava* flesh tissue hydrolysate (SFTH) dry powder.

Subjects and experimental design

Patients were eligible for inclusion if they were aged 30-80 years, had T2DM and hypertension with a systolic blood pressure (SBP) of 180 mmHg or less, diastolic blood pressure (DBP) of 110 mmHg or less, hemoglobin A_{1c} (HbA_{1c}) of 10% or less, triglyceride count of 1,000 mg/dL or less, low density lipoprotein (LDL)-cholesterol of 190 mg/dL or less at enrollment, and were taking a stable dose and type of antihypertensive, anti-diabetic, or other medications at the discretion of the responsible physician within 3 months. Exclusion criteria were pregnancy, known psychiatric diseases or drug abuse, type 1 diabetes, secondary hypertension or SBP ≥ 180 mmHg or DBP ≥ 110 mmHg, cardiovascular disorders (unstable angina pectoris, heart failure, history of myocardial infarction or cerebrovascular diseases within 6 months, and life-threatening arrhythmia), chronic kidney disease stage > 3, proteinuria ≥ 3.5 g/day, other severe systemic illnesses, and inability to communicate and comply with all study requirements. The Jeju National University Hospital's institutional review board approved the protocol (approval number: 2011-40), and informed written consent was obtained from all participants. The study was conducted by the Declaration of Helsinki, and performed in accordance with the International Conference on Harmonization (ICH) guidelines.

Eligible subjects were randomized within 2 weeks of the screening visit. The randomization codes were computer generated by a research coordinator in blocks to ensure an approximate balance (1:~1.5 ratio) between the placebo and SFTH treatment arms. If a subject was assigned a subject number, but did not receive study medication, the subject number was not used again. For randomization, we tried to match each subject with a control of similar age, sex, initial HbA_{1c} level, and BP at visit 1, and randomized consecutively. However, because paired comparisons between before and after treatments were possible for the investigating agent, the matching processes were not too strict. A SFTH dosage of 500 mg 1 time/day was chosen for the study. *S. clava* flesh tissue hydrolysate in 250 mg capsules was used based on previous *in vivo* tests and dosages in prior clinical studies. All subjects were instructed to ingest the capsules before a meal over a 4 week period. The vehicle-containing placebo was comparable in size and shape to the SFTH. All subjects were instructed to maintain their usual dietary intake and physical activity. Energy and food intake was not limited throughout the trial period, but supplemental food products containing *S. clava* were prohibited. Anthropometric parameters were measured at baseline. Blood sampling for efficacy and safety parameters was performed at baseline and at week 4.

Study measurements

SBP and DBP were measured by office BP monitoring at baseline and after 4 weeks. The BP measurements were conducted by a trained clinical research nurse in the seated position, with feet on the floor and the arm supported at heart level after at least 5 min of rest. The BP measurement that was used was the mean of two values recorded 3 minutes apart. Elevated values were confirmed on a separate day. Blood samples were collected at baseline and follow-up for measurement of the plasma concentrations of HbA_{1c}, lipoprotein, fructosamine, white blood cells (WBCs), hemoglobin, platelets, fibrinogen, total cholesterol, aspartate aminotransferase (AST), alanine transferase (ALT), sodium, potassium, chloride, total calcium, fasting blood glucose, gamma-glutamyl transpeptidase (GTP), triglycerides, HDL-cholesterol, LDL-cholesterol, high sensitivity C-reactive protein (hs CRP), apolipoprotein A1, apolipoprotein B, and insulin, and all samples were analyzed using routine automated methods. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using serum fasting glucose and insulin levels [12]. Urine samples were collected for measurement of albumin and creatinine, and the urine albumin-creatinine ratio (UACR) was calculated (mg/g of creatinine). Safety was evaluated through the collection of adverse experience reports, vital signs, and laboratory tests, which included hematology and blood chemistry analysis. Efficacy, safety, and all other laboratory measurements were conducted at Jeju National University Hospital (Jeju, Korea) by investigators and their trained members, all of whom were blinded to the treatment group.

Statistical analysis

The values of all test parameters are presented as the means ± standard error (SE). Paired *t*-tests or Wilcoxon signed-rank

tests were used to assess the differences before and after administration of the investigational products within groups using a per-protocol analysis. Moreover, between-group differences were assessed by independent samples *t*-tests if normally distributed and by non-parametric Mann-Whitney *U* tests otherwise. All statistical analyses were performed using the statistical analysis system (SAS) software (version 9.1.3, SAS Institute, Cary, North Carolina, USA). Statistical significance was considered at $P < 0.05$ and $P < 0.01$.

RESULTS

Clinical characteristics

From a total of 80 screened patients, 57 were randomized. One patient was excluded because she withdrew her consent before taking the investigating agent; thus, 56 patients [placebo ($n = 22$); SFTH ($n = 34$)] were subjected to analysis (Fig. 1). Baseline patient characteristics were age, gender, bodyweight, duration of diabetes, biochemical and hematological parameters and BP in both groups (Table 1). Baseline age, gender, body weight, duration of diabetes, biochemical and hematological parameters did not differ significantly between the two groups; however, baseline SBP and DBP did ($P = 0.006$ and $P = 0.022$, respectively).

Blood pressure control

The changes in SBP and DBP values in placebo and SFTH groups from baseline after 4 weeks are shown in Fig. 2. There were no significant differences in SBP and DBP between the two groups after 4 weeks of treatment. The SFTH group showed a significant decrease in both SBP and DBP ($P < 0.01$ each), whereas the placebo group did not show significant changes in either SBP or DBP after 4 weeks.

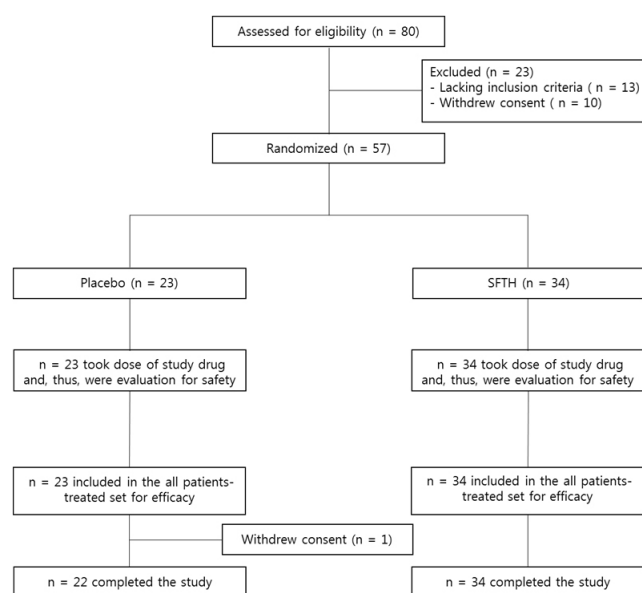


Fig. 1. Flow diagram of study patients. Detailed protocols of enrollment, allocation and follow-up research were introduced.

Table 1. Baseline characteristics.

Characteristics	Placebo (n = 22)	SFTH ¹⁾ (n = 34)	P-value
Age (yrs)	60.6 ± 1.9	58.2 ± 2.0	0.344
Duration of diabetes (months)	57.6 ± 13.7	75.2 ± 14.5	0.332
Gender (female: male)	13:10	17:17	-
Body weight (kg)	70.4 ± 3.1	71.1 ± 2.9	0.860
Waist circumference (cm)	94.18 ± 3.1	90.85 ± 1.67	0.223
SBP (mmHg)	140.2 ± 1.7	147.2 ± 1.6**	0.006
DBP (mmHg)	84.5 ± 1.5	89.2 ± 1.2*	0.022
Fasting serum glucose (mg/dL)	150.2 ± 7.3	136.6 ± 7.2	0.212
HbA _{1c} (%)	7.67 ± 0.20	7.58 ± 0.25	0.810
Fructosamine (μM)	314.9 ± 7.7	305.5 ± 10.4	0.510
UACR (mg/g of Cr)	155.2 ± 31.3	271.8 ± 57.1	0.136
Total cholesterol (mg/dL)	158.4 ± 6.6	160.3 ± 5.7	0.825
Triglycerides (mg/dL)	152.7 ± 34.2	144.0 ± 22.1	0.822
HDL-cholesterol (mg/dL)	46.8 ± 1.7	48.7 ± 2.3	0.550
LDL-cholesterol (mg/dL)	90.0 ± 5.6	92.1 ± 4.8	0.777
Apolipoprotein A1 (mg/dL)	142.9 ± 3.1	140.3 ± 4.6	0.688
Apolipoprotein B (mg/dL)	115.4 ± 7.7	114.0 ± 5.5	0.888
AST (IU/L)	22.3 ± 1.5	26.6 ± 3.0	0.724
ALT (IU/L)	28.3 ± 3.1	30.0 ± 4.3	0.208
Albumin (g/dL)	4.2 ± 0.05	4.3 ± 0.04	0.740
BUN (mg/dL)	18.4 ± 1.4	16.4 ± 1.1	0.289
Creatinine (mg/dL)	1.06 ± 0.04	1.05 ± 0.03	0.944
CKD-EPI (mL/min/1.73 m ²)	67.30 ± 3.04	69.19 ± 2.49	0.632
Insulin (μU/mL)	16.4 ± 4.8	16.9 ± 4.1	0.931
HOMA-IR	6.7 ± 2.2	5.6 ± 1.34	0.670
WBC (10 ³ /mL)	6.61 ± 0.42	6.77 ± 0.32	0.298
hsCRP (mg/dL)	0.18 ± 0.03	0.24 ± 0.08	0.615
Fibrinogen (mg/dL)	289.2 ± 16.7	309.3 ± 9.06	0.298
Metabolic syndrome ratio (%)	37.5	50	-

Data expressed as mean ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, hemoglobin A_{1c}; UACR, urine albumin-Cr ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; CKD-EPI, chronic kidney disease epidemiology collaboration; HOMA-IR, homeostasis model assessment of insulin resistance; WBC, white blood cells; hsCRP, high sensitivity C-reactive protein. ¹⁾ SFTH: *S. clava* flesh tissue hydrolysate; Comparisons between SFTH and placebo group (independent samples *t*-test): * $P < 0.05$ and ** $P < 0.01$.

Biochemical and hematological parameters

The changes in biochemical and hematologic parameters in the two groups are shown in Table 2. For some parameters, there were slight time differences within the two groups after

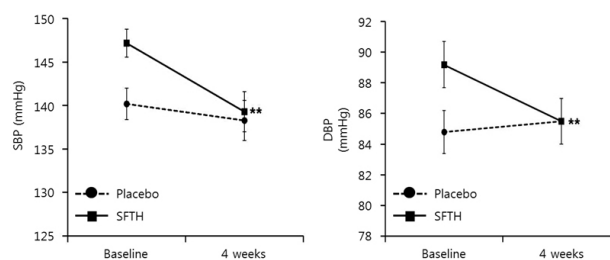


Fig. 2. Changes in SBP and DBP from baseline to 4 weeks for placebo and SFTH groups. SBP, systolic blood pressure; DBP, diastolic blood pressure; SFTH, *S. clava* flesh tissue hydrolysate. Statistical significance of the differences in the SFTH group is marked with the following symbol: ** $P < 0.01$.

Table 2. Changes in patient characteristics at 4 weeks.

Parameters	Placebo		SFTH ¹⁾	
	Basal	4 weeks ²⁾	Basal	4 weeks ^{3),4)}
Body weight (kg)	70.4 ± 3.1	69.9 ± 3.0*	71.1 ± 2.9	70.1 ± 2.8
HbA _{1c} (%)	7.67 ± 0.20	7.57 ± 0.22	7.5 ± 0.2	7.3 ± 0.1 ^{##}
Lipoprotein (a) (mg/dL)	28.8 ± 7.1	29.7 ± 6.9	46.7 ± 7.4	49.5 ± 7.4
Fructosamine (μM)	314.9 ± 7.7	311.5 ± 9.9	303.9 ± 9.4	298.2 ± 8.6
WBC (× 10 ³ /μL)	6.61 ± 0.42	6.55 ± 0.35	6.77 ± 0.32	6.32 ± 0.20 [#]
Hemoglobin (g/dL)	14.1 ± 0.4	15.3 ± 1.3	13.6 ± 0.2	13.6 ± 0.2
Platelet (× 10 ³ /μL)	225.3 ± 11.9	232.8 ± 14.2	230.0 ± 8.3	230.0 ± 8.2
Fibrinogen (mg/dL)	289.2 ± 16.7	300.5 ± 16.8	310.2 ± 9.5	329.0 ± 12.9
Protein (g/dL)	7.05 ± 0.09	7.07 ± 0.09	7.1 ± 0.1	7.1 ± 0.1
Albumin (g/dL)	4.2 ± 0.05	4.3 ± 0.06	4.3 ± 0.1	4.3 ± 0.1
Total cholesterol (mg/dL)	158.4 ± 6.6	157.3 ± 7.1	160.3 ± 5.7	161.5 ± 7.7
AST (IU/L)	22.3 ± 1.5	20.7 ± 1.1	26.6 ± 3.0	26.8 ± 3.1
ALT (IU/L)	28.3 ± 3.1	26.3 ± 2.5	30.0 ± 4.3	34.6 ± 7.5
BUN (mg/dL)	18.4 ± 1.4	18.1 ± 1.0	16.4 ± 1.1	15.4 ± 0.6 [†]
Creatinine (mg/dL)	1.06 ± 0.04	1.03 ± 0.04	1.05 ± 0.03	1.06 ± 0.03
CKD-EPI (mL/min/1.73 m ²)	67.30 ± 3.04	68.49 ± 2.32	69.19 ± 2.43	68.54 ± 2.43
Sodium (mmol/L)	139.4 ± 0.6	140.0 ± 0.5	140.6 ± 0.5	139.9 ± 0.4
Potassium (mmol/L)	4.1 ± 0.1	4.2 ± 0.1	4.2 ± 0.6	4.2 ± 0.5
Chloride (mmol/L)	102.5 ± 0.4	102.6 ± 0.4	102.2 ± 0.4	102.4 ± 0.4
Total calcium (mg/dL)	9.1 ± 0.1	9.1 ± 0.1	9.1 ± 0.1	9.2 ± 0.1
Glucose (mg/dL)	150.2 ± 7.3	156.8 ± 12.5	135.0 ± 6.8	134.5 ± 6.5
gamma-GTP (U/L)	44.4 ± 6.9	44.7 ± 7.3	43.0 ± 6.4	37.3 ± 5.0
Triglyceride (mg/dL)	152.7 ± 34.2	112.0 ± 12.4	144.0 ± 22.1	116.7 ± 10.5
HDL-cholesterol (mg/dL)	46.8 ± 1.7	47.5 ± 2.1	48.7 ± 2.3	48.4 ± 2.2
LDL-cholesterol (mg/dL)	90.0 ± 5.6	91.5 ± 6.0	92.1 ± 4.8	96.5 ± 5.8
hsCRP (mg/dL)	0.18 ± 0.03	0.17 ± 0.04	0.24 ± 0.08	0.30 ± 0.10
Apolipoprotein A1 (mg/dL)	142.9 ± 3.1	140.0 ± 4.3	140.3 ± 4.6	139.2 ± 4.8
Apolipoprotein B (mg/dL)	115.4 ± 7.7	105.4 ± 6.4	114.0 ± 5.5	102.1 ± 4.5
Insulin (μU/mL)	16.4 ± 4.8	16.9 ± 7.7	16.9 ± 4.1	9.2 ± 0.9
UACR (mg/g Cr)	160.7 ± 30.4	286.5 ± 70.1*	281.0 ± 60.2	318.3 ± 93.4
HOMA-IR	6.7 ± 2.2	8.8 ± 5.2	5.6 ± 1.3	3.1 ± 0.4
Metabolic syndrome ratio (%)	37.5	52.1	50	44.1

Data are expressed as the means ± SE. HbA_{1c}, hemoglobin A_{1c}; WBC, white blood cells; AST, aspartate transaminase; ALT, alanine transaminase; BUN, blood urea nitrogen; CKD-EPI, chronic kidney disease epidemiology collaboration; GTP, glutamyl transpeptidase; HDL, high density lipoprotein; LDL, low density lipoprotein; hsCRP, high sensitivity C-reactive protein; UACR, urine albumin-creatinine ratio; HOMA-IR, homeostasis model assessment of insulin resistance.

¹⁾ SFTH: *S. clava* flesh tissue hydrolysate

²⁾ Comparison made between basal and 4 weeks in placebo group (paired *t*-test): * *P* < 0.05

³⁾ Comparison made between basal and 4 weeks in SFTH group (paired *t*-test): # *P* < 0.05 and ## *P* < 0.01.

⁴⁾ Comparison made between placebo and SFTH group (independent samples *t*-test): † *P* < 0.05.

Table 3. Summary of adverse events in the study.

	Placebo (n = 22)	SFTH ¹⁾ (n = 34)
Adverse event, n (%)	6 (26.1)	4 (11.8)
Pruritus	1 (4.3)	3 (8.8)
Heartburn	2 (8.7)	-
Diarrhea	-	1 (2.9)
Inosomnia	1 (4.3)	-
Dyspepsia	12 (8.7)	-
Serious adverse event, n (%)	0	0
Discontinuation due to adverse event, n (%)	0	0

¹⁾ SFTH: *S. clava* flesh tissue hydrolysate

4 weeks of treatment, but there were no significant differences between groups at 4 weeks. However, blood urea nitrogen

(BUN) differed significantly (*P* = 0.039) between the two groups after the 4 week. The SFTH group exhibited significant decreases in HbA_{1c} level (*P* = 0.008) and WBC count (*P* = 0.048) after 4 weeks as well as a tendency toward improvement in the levels of circulating triglyceride, apolipoprotein B, insulin and HOMA-IR index after 4 weeks. The body weight in the placebo group (*P* = 0.033) after 4 weeks, while the UACR was increased. As shown in Table 3, neither group showed serious adverse events, and there were no discontinuations associated with adverse events in either group. The number of patients with abnormal laboratory findings was low and similar between treatment groups. In addition, there were no clinically relevant changes in physical status, vital signs, or electrocardiography (ECG) observed.

DISCUSSION

Many marine bioresources have recently been investigated for their ability to improve metabolic syndromes, such as obesity, diabetes and hypertension [13-17]. Among these, the sea squirt, *Styela clava*, which is rich in proteins, polyunsaturated fatty acid, fibers, and carotenoids, is known to have a high nutritional value and is therefore commonly used as a food ingredient in Korea [18]. Among the compositions of *S. clava* tissue, the flesh tissue protein is more than 65%, which is two times higher than that of tunic tissue [19]. Therefore, flesh tissue proteins can be converted into bioactive peptides by enzymatic hydrolysis, which can therefore be used to enhance the biological activities of flesh tissue proteins. We previously reported that the enzymatic hydrolysates from *S. clava* flesh tissue protein has the potential to reduce BP via ACE inhibition and NO generation to induce endothelial vasodilation [10,11]. However, the antihypertensive effects of this food itself or its ingredients have not been evaluated in human subjects. Therefore, the present study was conducted to investigate the antihypertensive effect and safety of enzymatic hydrolysate from *S. clava* flesh tissue protein in Korean patients with hypertension and T2DM. In this double-blind, randomized, placebo-controlled clinical study, after a 4-week administration of SFTH, favorable changes in SBP, DBP and some metabolic parameters were detected in subjects who consumed 500 mg/day SFTH without any noticeable adverse effects.

ACE inhibition and NO generation are important factors in lowering blood pressure [20,21]. Among the regulatory factors related to hypertension, ACE regulates BP by KKS and RAS [22]. Moreover, NO-mediated vasorelaxation is one of the mechanisms of antihypertensive effects [10]. Previous studies have shown that spontaneously hypertensive rats (SHRs) treated with the peptides from *S. clava* decreased SBP level, inhibited ACE and generated NO production in the vascular endothelium [10,11], suggesting that *S. clava* could regulate BP via ACE inhibition and NO generation.

Control of high BP is very important for primary and secondary prevention of cardiovascular diseases, the prevalence and risk of which are increased in patients with diabetes, atherosclerosis and hyperlipidemia [13]. Hypertension is also commonly associated glucose intolerance, and poses a major threat to human health worldwide [23,24]. It has been reported that ACE inhibition plays a role in glucose homeostasis in subjects with diabetes [24]. In our previous studies, we purified an ACE inhibitory peptide from *S. clava* flesh tissue [7] and demonstrated its stimulating effect on glucose uptake in skeletal muscle cells via AMP-activated protein kinase (AMPK) activation [23]. In the SFTH group, serum levels of triglyceride, apolipoprotein B, insulin and the HOMA-IR index tended to be improved after 4 weeks. This finding may partially explain the effects of SFTH on BP and HbA_{1c}, although blood glucose did not change significantly. Moreover, both groups had low incidences of adverse events and were similar to the two groups. Based on the overall results, the use of SFTH or the intake of the sea squirt *S. clava* might be beneficial to patients with cardiometabolic diseases. The SFTH used in this study is considered relatively safe because it used food grade enzyme. However, further studies are needed

to confirm its potent antihypertensive effects, as well as the adverse effects associated with long-term use of SFTH in more hypertensive patients than were included in this study. In addition, it has previously been reported that excess daily salt intake impairs vasorelaxation and vasoconstriction, resulting in increased BP [25]. Accordingly, these results support the further evaluation of the salt intake via urine sodium and urine creatinine.

In conclusion, the present study showed that SFTH has antihypertensive effects with some metabolically beneficial effects in patients with T2DM and hypertension. Thus, SFTH might be a promising pharmaceutical resource that will be helpful to control cardiometabolic diseases.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interests.

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