



Improvement of Blood Pressure, Glucose Metabolism, and Lipid Profile by the Intake of Powdered Asparagus (蘆筍 *Lú Sǔn*) Bottom-stems and Cladophylls

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ABSTRACT

Asparagus (蘆筍 *Lú Sǔn*; *Asparagus officinalis* L.) is a common vegetable, long used as an herbal medicine. The cladophylls and bottom-stems of asparagus have various pharmacological effects, but they are generally discarded at harvesting. The present open clinical trial was performed to examine the effects of the intake of cladophylls and bottom-stems on the improvement of metabolic syndrome characterized by hypertension, hyperglycemia, and dyslipidemia. Twenty-eight healthy volunteers ingested either cladophyll or bottom-stem powder (6 g/day) daily for 10 weeks. The cladophyll intake resulted in significant reduction in the subjects' diastolic blood pressure and fasting plasma glucose (FPG), and decreased both the left cardio-ankle vascular index score and the total cholesterol level (T-CHO). The bottom-stem intake significantly reduced the subjects' systolic and diastolic blood pressure and FPG as well as T-CHO. These results suggest the possibility that asparagus cladophylls and bottom-stems differentially improve hypertension, hyperglycemia, and dyslipidemia.

Key words: Asparagus, Cardio-ankle vascular index, Cladophyll, Dyslipidemia, Hypertension, Hyperglycemia

INTRODUCTION

Asparagus (蘆筍 *Lú Sǔn*; *Asparagus officinalis* L.) is a healthy and nutritious vegetable that is consumed in many countries. Historically, asparagus has been used as a traditional medicine in China as an antifebrile and antitussive agent, hair growth stimulator, and diuretic agent.^[1] A recent study indicated that asparagus and its extracts have potential in terms of anti-fungal, anti-dyspeptic, antihypertensive, antidyplipidemic, and antihyperglycemic effects.^[2]

However, the mechanisms of these effects have not been fully elucidated.

Various bioactive compounds, including flavonoids, sterol-saponins, oligosaccharides, and carotenoids, have been identified in asparagus.^[3-6] A large amount of rutin was found in asparagus, at a level similar to that of buckwheat;^[7] rutin is a flavonol glycoside composed of the flavonol quercetin and the disaccharide rutinose.^[8] The main biological activity associated with rutin and quercetin is the antioxidant effect through a free radical scavenging capacity.

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DOI: 10.4103/2225-4110.119728

^[9] It has also been reported that rutin has various effects *in vitro* and *in vivo*, including anti-inflammatory, antihypertensive, and antihyperglycemic effects.^[10-12]

The edible shoot of asparagus is about one-half to two-thirds of the full length of the stems. When asparagus stems are cropped, leaf-like ferns called cladophylls and the remaining woody part (the bottom-stem) are removed and discarded as by-products because they are tough and difficult to eat. Motoki *et al.* reported that an estimated 130,000 kg of asparagus cladophylls is annually discarded as industrial waste.^[13] However, the cladophylls contain a variety of bioactive substances. Approximately three times the amount of rutin was identified in asparagus cladophyll compared to the green asparagus stem.^[14] It was reported that asparagus bottom-stems contain protodioscin, an antitumor substance, at a level over 100 times that seen in the green asparagus stems.^[15] These findings indicate that the by-products of asparagus, such as cladophyll and bottom-stem, could be used as the sources of several functional ingredients for supplements to improve metabolic syndrome, which is characterized by hypertension, hyperglycemia, and dyslipidemia.

In this study, we evaluated the effects of asparagus bottom-stems and cladophylls in human beings by analyzing the biomarkers associated with blood glucose metabolism as well as the lipid profile in healthy subjects.

METHODS

Study subjects and protocol

The study population consisted of 28 volunteers (14 males and 14 females, aged 35–67 years). We recruited those volunteers whose body mass index (BMI) ranged from 20 to 30 kg/m². Among them, 17 volunteers were diagnosed as having metabolic syndrome or pre-metabolic syndrome according to the diagnostic criteria of The Japan Society for the Study of Obesity (JASSO).^[16]

None had a history of recent gastrointestinal illness, pregnancy, significant disease, surgery, or severe allergic reactions to food, or current use of any medications or supplements. The 28 subjects were randomly and blindly divided into two treatment groups ($n = 14$ each): the cladophyll group and the bottom-stem group. All subjects took 6 g of cladophyll or bottom-stem powder daily for 10 weeks. The dosage and follow-up period were determined considering the results of both an experimental animal study with rats and a pilot clinical trial with human beings (data not shown). The subjects were advised to ingest the powder either with a glass of water or as an ingredient in their cooking. Measurements of blood pressure (BP) and the cardio-ankle vascular index (CAVI) score were performed at baseline (0 week), 5 weeks, and 10 weeks after the initiation of the powder supplementation. Biomarkers for glucose and lipid metabolisms were measured at 0 week and 10 weeks.

The protocol for this study was approved by the Ethics Committee for Human Health of Hokkaido Information University, and written informed consent was obtained from all subjects. The study was carried out in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

Test meal preparation

The powdered cladophylls and bottom-stems of green asparagus (蘆筍 *Lú Sūn*; *Asparagus officinalis* L.) harvested in Hokkaido were kindly provided by Hokushin Foods Co. Ltd (Ebetsu, Hokkaido, Japan). Dry powder of cladophylls was prepared by blanching, drying and crushing cladophylls in a conventional method. In a similar manner, bottom-stem powder was prepared by blanching, drying and crushing the bottom-stem, and the powder was mixed with trehalose and dextrin (bottom-stem powder:trehalose:dextrin = 1:1:7). The production and the packing were carried out in Hokushin Foods Co. Ltd, the quality-controlled manufacturing plant in compliance with the Food Sanitation Act (the Ministry of Health, Labor, and Welfare of Japan). The quality and safety of test samples were thoroughly examined by Hokushin Foods Co. Ltd.

Measurement of BP and CAVI score

The subjects' CAVI and BP values were measured at each visit under carefully controlled conditions by means of the VaSera CAVI instrument (Fukuda Denshi Co., Tokyo, Japan). To measure the CAVI, cuffs were placed on both ankles and brachium. In brief, CAVI was calculated using the following formula: $CAVI = a \{ (2q/DP)^9 \ln(Ps/Pd)PWV^2 \} + b$, where Ps is the systolic blood pressure (SBP), Pd is the diastolic blood pressure (DBP), PWV is the pulse wave velocity (Hasegawa's method), DP is Ps – Pd, q is blood density, and a and b are constants.

Statistical analysis

Averages and standard deviations of age and other parameters were calculated for each group. Statistical analyses were performed with the program IBM SPSS Statistic 19 (IBM, Armonk, NY, USA). Paired *t*-tests were performed for the data obtained at baseline and at 5 weeks and 10 weeks after the supplementation started. *P*-values less than 0.05 were considered as significant.

RESULTS

Effect of cladophyll and bottom-stem on BP

Twenty-seven subjects (13 males and 14 females) completed the study; one male subject dropped out due to his irregular diet. The clinical characteristics of all subjects are shown in Table 1. First, to determine the effect of the cladophyll and bottom-stem powder on BP, we measured SBP and DBP. We found that bottom-stem intake significantly reduced SBP from 143.2 ± 6.1 mmHg to

Table 1. Characteristics of the subjects in the asparagus bottom-stem and cladophyll groups

Characteristic	Bottom-stem	Cladophyll
Number of subjects	14	13
Age (years)	50.86 ± 10.57	50.38 ± 9.25
Number of males (%)	9 (64.29%)	8 (61.54%)
Body weight (kg)	67.73 ± 10.07	69.06 ± 10.94
Height (cm)	164.18 ± 7.66	164.36 ± 8.58
Body mass index (kg/m ²)	25.04 ± 2.85	25.51 ± 3.17

Values shown are mean ± SD. Statistical analysis was performed by paired *t*-test for age, body weight, height, and body mass index, and by chi-square test for gender

135.7 ± 6.5 mmHg ($P = 0.031$) in 5 weeks after the ingestion and from 143.2 ± 6.1 mmHg to 134.6 ± 4.4 mmHg ($P = 0.012$) in 10 weeks after the ingestion [Figure 1a]. A significant improvement was also observed in DBP after 10 weeks of intake of both cladophyll and bottom-stem, showing reduction from 80.6 ± 2.1 mmHg to 75.2 ± 2.5 mmHg ($P = 0.015$) and from 86.0 ± 3.7 mmHg to 81.4 ± 3.5 mmHg ($P = 0.040$), respectively [Figure 1b]. Moreover, we observed that DBP in 5 weeks after the bottom-stem intake was significantly decreased from 86.0 ± 3.7 mmHg (the baseline) to 80.1 ± 3.1 mmHg (5 weeks) ($P = 0.004$).

Effect of cladophyll and bottom-stem powder ingestion on CAVI scores

We also examined the subjects' CAVI scores on both ankles

and brachium. The CAVI score has been widely accepted as a reliable indicator of arterial stiffness.^[17] The subjects' right CAVI scores showed little change, but the left CAVI scores appeared to be slightly decreased from 7.19 ± 0.19 to 6.95 ± 0.19 after the cladophyll intake, which was a non-significant reduction ($P = 0.26$) [Figure 2].

Effects of cladophyll and bottom-stem on glucose metabolism

We next examined the effects of cladophyll and bottom-stem powder ingestion on fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c). Although no significant change in the subjects' HbA1c values was observed [Figure 3b], the FPG values were significantly decreased by both bottom-stem and cladophyll intake, from 104.1

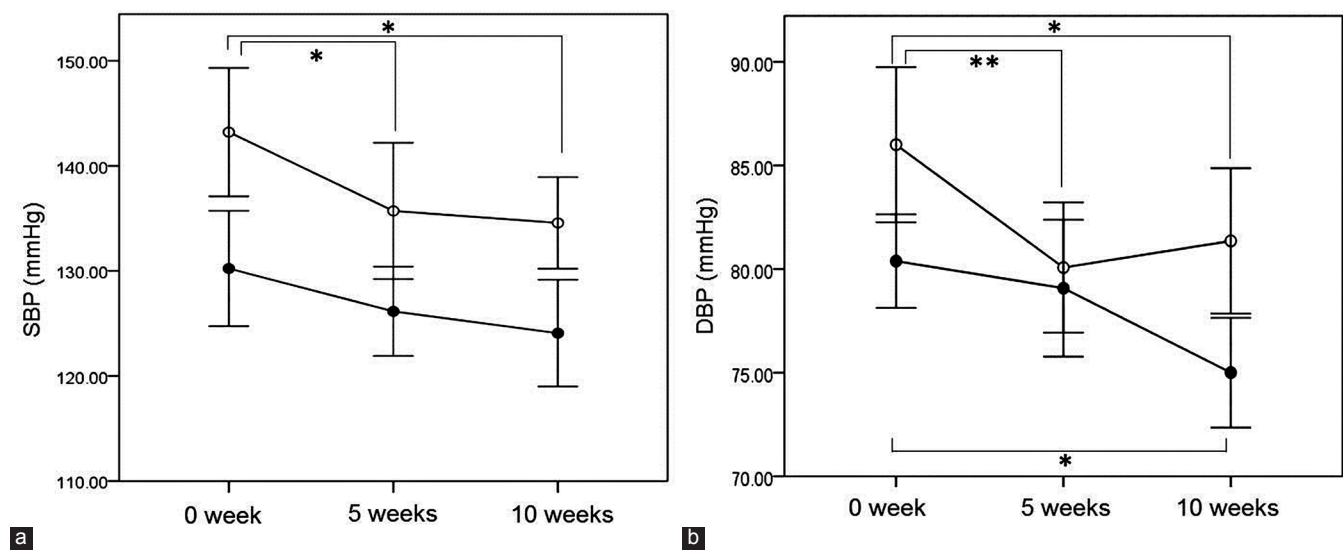


Figure 1. Changes in the subjects' blood pressure following the 10-week daily intake of 6 g of asparagus bottom-stem or cladophyll powder. Values are means ± SE. (a) Systolic blood pressure (SBP), (b) diastolic blood pressure (DBP). Open circles, bottom-stem subjects ($n = 14$); closed circles, cladophyll subjects ($n = 13$). * $P < 0.05$, ** $P < 0.01$

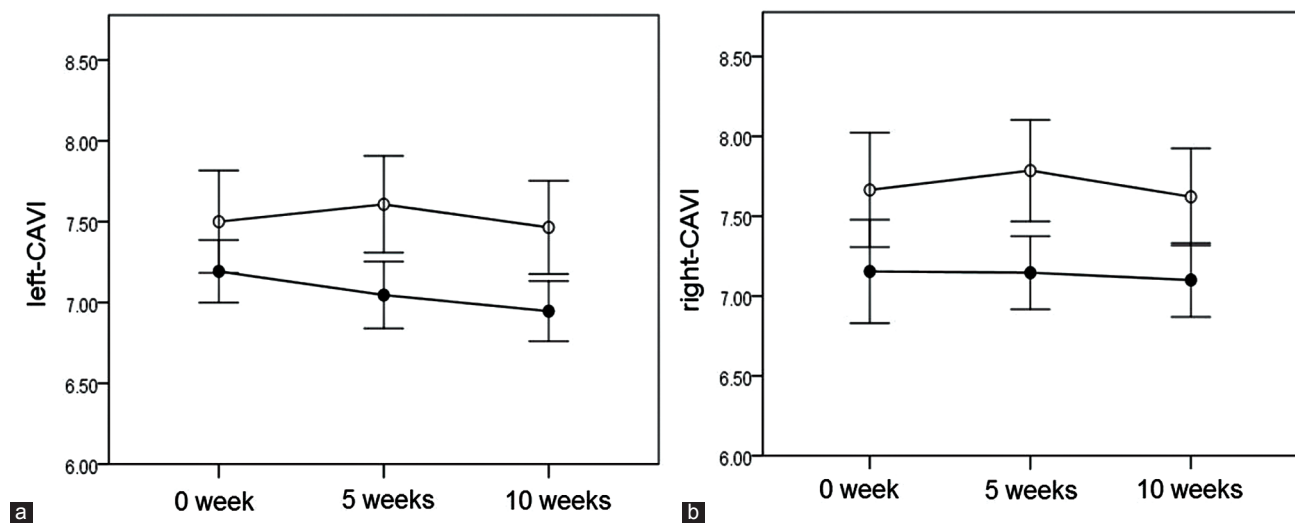


Figure 2. Effect of bottom-stem and cladophyll intake on the cardio-ankle vascular index (CAVI) scores. Values are means ± SE. (a) Left CAVI, (b) right CAVI. Open circles, bottom-stem subjects ($n = 14$); closed circles, cladophyll subjects ($n = 13$)

± 3.7 mg/dl to 100.9 ± 3.4 mg/dl ($P = 0.042$) and from 109.5 ± 4 mg/dl to 102.9 ± 2.9 mg/dl ($P = 0.037$), respectively [Figure 3a].

Effects of cladophyll and bottom-stem on lipid metabolism

We measured the total cholesterol (T-CHO) and triglycerides (TG). As shown in Figure 4, we found minimal changes in TG levels, but the bottom-stem ingestion significantly decreased the T-CHO levels from 240.4 ± 6.5 mg/dl to 227.2 ± 8.3 mg/dl ($P = 0.028$). The T-CHO levels also tended to decrease after cladophyll intake, from 222.5 ± 8.1 mg/dl to 215.2 ± 9 mg/dl ($P = 0.302$).

Biomarker levels of liver and renal functions after cladophyll and bottom-stem intake

We also examined the subjects' serum levels of biomarkers of liver and renal function. Parameters for liver function, i.e.,

aspartate transaminase (AST), alanine transaminase (ALT), and gamma glutamyl transpeptidase (γ -GTP), and those for renal function, i.e., blood urea nitrogen (BUN) and creatinine, showed minimal changes after the 10-week powder intake, suggesting that cladophyll and bottom-stem intake causes no unfavorable effects on the liver and kidneys at the dose of 6 g/day.

DISCUSSION

A definition of metabolic syndrome was first provided by the World Health Organization (WHO) in 1998.^[18] The International Diabetes Foundation estimated that approximately 20–25% of the world's adult population has metabolic syndrome.^[18] Metabolic syndrome comprises a cluster of metabolic abnormalities

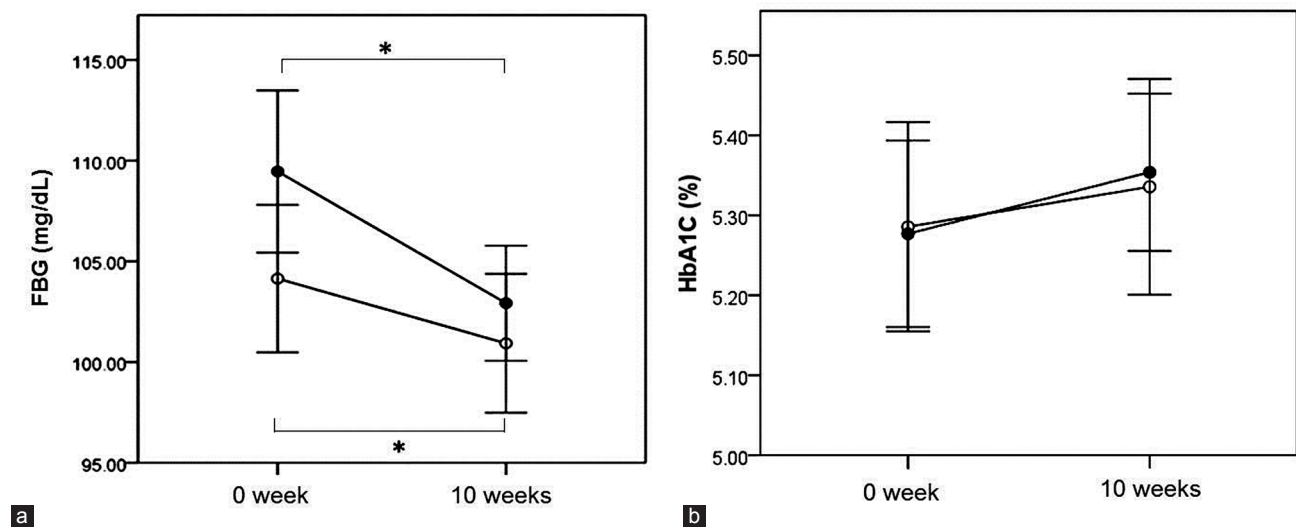


Figure 3. Changes in blood glucose metabolism produced by the intake of powdered asparagus bottom-stems and cladophylls. Value are means \pm SE. (a) Fasting plasma glucose (FBG), (b) hemoglobin A1c (HbA1c). Open circles, bottom-stem subjects ($n = 14$); closed circles, cladophyll subjects ($n = 13$). * $P < 0.05$

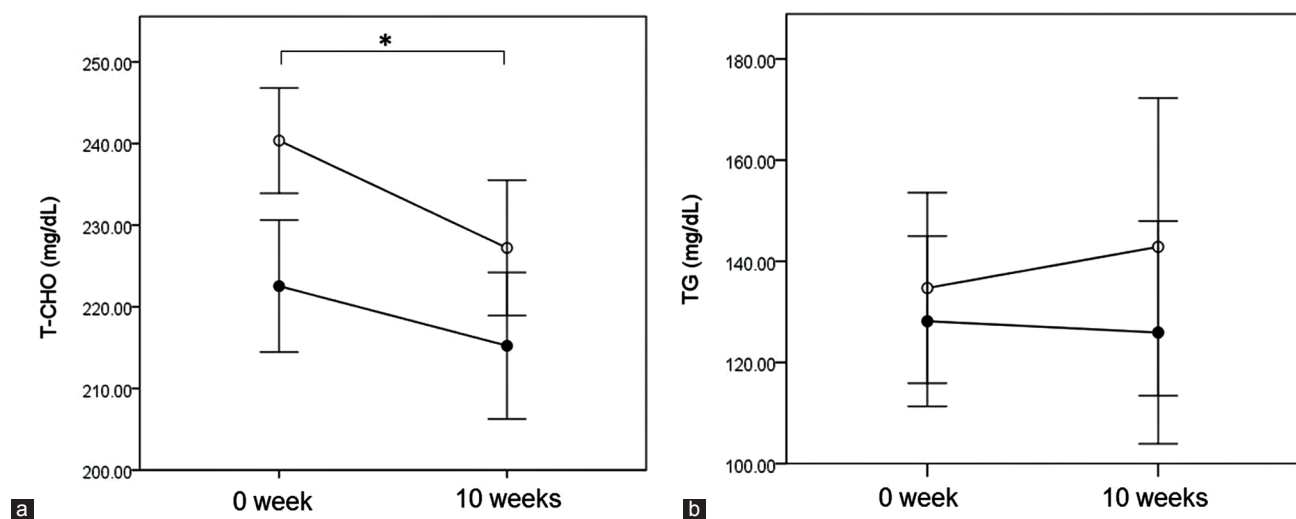


Figure 4. Changes in the subjects' serum lipid profiles in response to the intake of bottom-stems and cladophylls. (a) Total cholesterol (T-CHO), (b) triglycerides (TG). Value are means \pm SE. Open circles, bottom-stem subjects ($n = 14$); closed circles, cladophyll subjects ($n = 13$). * $P < 0.05$

including central obesity and high cholesterol, high SBP or DBP, and increased fasting glucose.^[19,20] Metabolic syndrome is a risk factor for cardiovascular disease, diabetes, and certain cancers.^[21]

The intake of nutritionally well-balanced health foods is the first clinical intervention to counteract metabolic syndrome. The routine intake of certain vegetables has been observed to reduce the risk of metabolic syndrome.^[22] A number of vegetables with potential bioactive components, such as polyphenols, sterols, oligosaccharides, and vitamins, have been investigated with regard to antihypertensive, antihyperlipidemic, and antihyperglycemic effects.^[23] Notably, some researchers have focused on the use of by-products of vegetables for supplementation and, thereby, evaluated them as a potential functional source.^[24]

The results of the present open clinical trial demonstrate the potential effect of cladophyll and bottom-stem of asparagus (蘆筍 *Lú Sūn*; *Asparagus officinalis* L.) in the prevention of hypertension, hyperglycemia, and dyslipidemia. We found that cladophyll and bottom-stem reduced BP and T-CHO. In particular, a reduction in FPG followed the 10-week intake of bottom-stem powder and cladophyll powder. These results suggest that asparagus cladophyll and bottom-stem have the potential to prevent and improve lifestyle diseases.

Hypertension is one of the major risk factors for stroke, congestive heart failure, myocardial infarction, peripheral vascular disease, and overall mortality.^[25] In the present study, significantly reduced DBP or SBP was observed, as demonstrated in Figure 1. Matsuda *et al.* demonstrated that asparagus stem prevented hypertension through inhibiting angiotensin-converting enzyme (ACE) activity in spontaneously hypertensive rat (SHR), and the 2"-hydroxynicotianamine contained in asparagus would be a critical component for this effect. It was also reported that rutin improved arterial hypertension in an animal model.^[26] To elucidate their functionality for these diseases, the quantification of 2"-hydroxynicotianamine and rutin contained in the asparagus bottom-stems and cladophylls used in the present study would be helpful. However, more than 10 mmHg difference of SBP between the two groups was found at the beginning of the trial (130.23 ± 19.80 mmHg for cladophylls and 143.21 ± 22.85 mmHg for bottom-stems, with no significant difference). This difference, even though statistically not significant, might influence the bottom-stems group show better improvement in SBP than the cladophylls group. In this context, further research is required to confirm the effect of cladophylls and bottom-stems on the prevention of hypertension.

Diabetes mellitus is caused by dysregulation of blood sugar that is characterized by persistent hyperglycemia even during the fasting state. A raised fasting serum glucose level is an early sign of impaired glucose tolerance that is widely used as a screening test for diabetes. Recently, extensive search for natural products with the potential to reduce blood glucose has been carried out in the field of traditional medicine, because the materials provided by traditional medicine are generally considered to be better than the currently used pharmaceuticals.^[27] In the present study, FBG was significantly reduced by cladophyll and bottom-stem intake, as shown in Figure 3.

There are some reports of the effect of asparagus in the prevention of hyperglycemia. For example, asparagus intake improved

insulin secretion and β -cell function *in vivo* and *in vitro*.^[28] Zhao *et al.* demonstrated that asparagus bottom-stem has hypoglycemic functions in a streptozotocin-induced diabetic rat model.^[29] These findings suggest that the by-products of asparagus we used in this study have similar biological effects in terms of glucose metabolism.

We also found that the asparagus bottom-stem intake significantly decreased the subjects' T-CHO levels, and the cladophyll intake also reduced the T-CHO levels, to a lesser extent. Dyslipidemia, a medical condition characterized by increased blood levels of lipids such as cholesterol and TG, is an essential component of metabolic syndrome and a predisposing risk factor for atherosclerosis. It is well recognized that lifestyle factors, especially dietary habits, play an important role in preventing the progress of dyslipidemia. In a hypercholesteremic rat model, Visavadiya *et al.* (2009) observed that asparagus bottom-stems contained food factors useful for the reduction of serum cholesterol by increasing the rats' bile acid production and elevating their hepatic antioxidant status.^[30] They also pointed out that the potent therapeutic phytochemicals present in asparagus bottom-stems, e.g., phytosterols, saponins, polyphenols, flavonoids, and ascorbic acid, are responsible for the improvement of hypercholesterolemia.

Although we did not investigate the mechanisms responsible for the biological activity of asparagus cladophyll and bottom-stem in the present study, we observed that T-CHO was significantly decreased by the cladophyll and bottom-stem intake. This result suggests that the by-products of asparagus could improve metabolic syndrome by reducing serum cholesterol. In addition, the cladophyll intake slightly decreased the subjects' left CAVI scores, as shown in Figure 2. CAVI is a blood pressure-independent arterial wall stiffness parameter widely used in clinical studies. Several reports have shown that CAVI is associated with atherosclerotic disease.^[31] Data from the present study and findings from a number of earlier studies strongly indicate that cladophyll may improve arteriosclerosis via a reduction in serum cholesterol.

In summary, we demonstrated the possibility that asparagus bottom-stems and cladophylls can modulate hypertension, hyperglycemia, and dyslipidemia in human beings, as shown in Figure 5. Although we need to obtain more detailed data including those of bioactive components, our observations suggest that the effec-

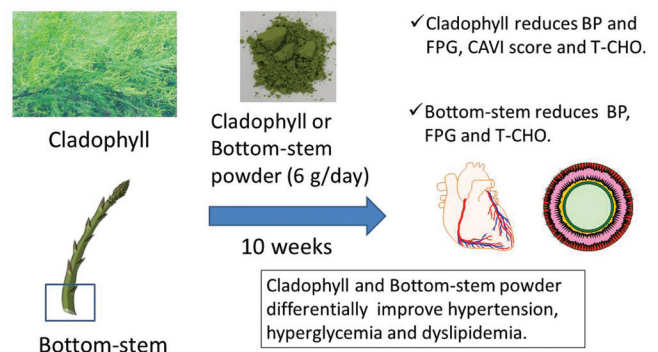


Figure 5. The potential effect of cladophyll and bottom-stem of asparagus for the prevention of hypertension, hyperglycemia, and dyslipidemia

tive use of asparagus bottom-stems and cladophylls may prevent lifestyle-related diseases, and the production of supplements containing these functional materials would be beneficial both for human beings and to eliminate the waste of these asparagus by-products.

ACKNOWLEDGMENTS

We are grateful to Ms. Aiko Tanaka, Rina Kawamura, Tomoko Mino, and Megumi Shibata for their technical assistance with the data management, and we thank Mr. Jungo Hayashi for his management of the clinical trial. This study was supported in part by the Organization of Hokkaido Food Innovation and the NOASTEC Foundation.

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