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A Mixed Green Vegetable and Fruit Beverage Decreased the Serum Level of Low-Density Lipoprotein Cholesterol in Hypercholesterolemic Patients

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The effects of a canned mixed green vegetable and fruit beverage, containing broccoli (*Brassica oleracea* L. var. *botrytis* L.) and cabbage (*Brassica oleracea* L. var. *capitata* L.) as main materials, on serum lipid levels in hypercholesterolemic patients were investigated. Thirty-one adult subjects were administered two cans of the beverage (160 g/can) per day for 3 weeks. Their serum total cholesterol (TC) levels significantly decreased from 6.7 $\pm$ 0.8 to 6.1 $\pm$ 0.6 mmol/L, and, more strikingly, the level of low-density lipoprotein cholesterol (LDL-C) significantly decreased from 4.4 $\pm$ 0.8 to 3.8 $\pm$ 0.7 mmol/L. At 9 weeks after the cessation of the administration, these levels had returned to the preadministration levels. Furthermore, 14 other subjects who were administered one can of the sample for 12 weeks also showed a significant reduction in the levels of serum TC and LDL-C. Thus, daily consumption of this mixed green vegetable and fruit beverage may be useful in lowering serum TC and LDL-C levels in hypercholesterolemic patients.

KEYWORDS: Mixed green vegetable and fruit beverage; broccoli (*Brassica oleracea* L. var. *botrytis* L.); cabbage (*Brassica oleracea* L. var. *capitata* L.); hypercholesterolemia; cholesterol-lowering effect; humans

INTRODUCTION

Although the onset and aggravation of hyperlipidemia are related to genetic factors, environmental factors, especially eating habits, have a strong influence on the disease. Hypercholesterolemia is considered to lead to atherosclerosis; the normalization of serum levels of low-density lipoprotein cholesterol (LDL-C) through diet therapy or administration of drugs decreases the incidence of coronary heart disease (CHD) (*1*, *2*). The clinical approach to primary prevention of CHD calls for lifestyle changes, including (1) reduced intakes of saturated fat and cholesterol, (2) increased physical activity, and (3) weight control (*2*).

The effects of food intake on the body's physiological functions are attracting considerable attention. Fruits and vegetables contain constituents, notably vitamins, minerals, and dietary fiber, essential to a healthy, well-balanced diet. Furthermore, it has been shown that some of the secondary metabolites of fruits and vegetables, such as flavonoids and carotenoids, are beneficial to health in directly combating the onset of cancer and CHD (*3*, *4*). Thus, a diet rich in vegetables and fruits may provide protection against cardiovascular disease, several common cancers, and other chronic diseases (*5*).

The hypocholesterolemic effects of vegetables and fruit and their constituents have been examined in some detail. Isolated dietary fibers from vegetable and fruit sources, especially pectins, have been shown to have hypocholesterolemic action in humans (*6*, *7*). The addition of fiber-containing foods to experimental diets also lowers plasma cholesterol to varying degrees (*8*−*10*).

In our previous studies (submitted) we have found that broccoli and its water extract significantly suppressed the increase of serum cholesterol levels in cholesterol-fed rats, and the hypocholesterolemic activity of broccoli was comparable to that of isolated soy protein (*11*). Also, we have been developing easier methods for serving daily for a long period a fixed amount of certain types of green vegetables and fruits, which may have beneficial health effects on human bodies. By examining the influence of the edible plant beverage on 20 healthy human volunteers in our preliminary study, we found that oral administration daily for 3 weeks of two cans (160

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Table 1. Energy and Known Nutrient Contents in One Can of Test Beverage[a]

energy and nutrient	amount	energy and nutrient	amount
energy, kJ	222	Mg, mg	13.9
protein, g	1.0	Zn, mg	0.395
fat, g	0.32	Cu, mg	0.073
nonfibrous carbohydrate, g	13	vitamin A efficacy, IU	80
		β-carotene, mg	0.133
dietary fiber, g	1.3	vitamin B_1, mg	0.03
cholesterol, mg	0	vitamin B_2, mg	0.05
Na, mg	35	niacin, mg	0.26
K, mg	326	vitamin C, mg	73
Ca, mg	32.2	vitamin D, mg	0
P, mg	24.7	vitamin E efficacy, mg	0.48
Fe, mg	0.24	SMCS,[b] mg	20

[a] One can of the test beverage contained 160 g. [b] SMCS, *S*-methylcysteine sulfoxide.

g/can) of a mixed green vegetable and fruit beverage, containing broccoli (*Brassica oleracea* L. var. *botrytis* L.) and cabbage (*Brassica oleracea* L. var. *capitata* L.) as main materials, significantly decreased the serum level of LDL-C in these subjects from 2.9 ± 0.7 to 2.5 ± 0.7 mmol/L (14% decrease) (*12*). However, there were only three volunteers whose serum levels of total cholesterol (TC) were >6.2 mmol/L included in the study. Thus, in the present study, the effects of the mixed green vegetable and fruit beverage on serum lipid levels in hypercholesterolemic patients whose TC levels were >6.2 mmol/L were investigated.

MATERIALS AND METHODS

Test Beverage. The beverage used in the test is a canned mixed green vegetable and fruit beverage containing a blend of green vegetables and fruits, which are broccoli, cabbage, celery (*Apium graveolens* L.), lettuce (*Lacutuca sativa* L.), spinach (*Spinacia oleracea* L.), parsley (*Petroselinum crispum*), komatsuna (*Brassica campestris* L. var. *komatsuna*), leaves of Japanese radish (*Raphanus sativus* L. var. *acanthiformis* Makino), apples (*Malus pumila* Miller**)**, and lemons (*Citrus limon* Burmann fil.). The beverage was prepared by Sunstar Inc. (Osaka, Japan), briefly described as follows. Broccoli and cabbage, other vegetables, and fruit (juice or puree) were mixed together in the ratio 36:19:45 and poured into cans. The cans were sealed, heated to 97 °C, and immediately cooled to room temperature. **Table 1** shows the nutrients contained in one can (160 g contents). The nutrient contents were analyzed according to *Analytical Manual of Standard Tables of Food Composition in Japan* (*13*). *S*-Methylcysteine sulfoxide (SMCS) was determined by means of HPLC methods (*14*).

Subjects. Forty-five subjects aged 22−59 years with hypercholesterolemia (>6.2 mmol/L of serum TC) were studied after giving their informed consent. The participants had no episodes of ischemic heart disease and did not receive any drug treatment. The patients were randomly divided into two separate study groups.

Study Design. In the first study (study A), 31 patients (20 males and 11 females, average age = 43.3 ± 10.9 years) were administered two cans of the test beverage per day in addition to their regular meals for a period of 3 weeks. The patients were asked to try not to change their lifestyles including eating and exercise habits during the testing period. A fasting blood sample was taken from each patient 12 weeks prior to and just before administration as baselines, and samples were taken again 3 weeks after the start of administration and 9 weeks after the cessation of administration.

In the second study (study B), 14 patients (8 males and 6 females, average age = 45.9 ± 11.1 years) were administered one can of the beverage per day for 12 weeks. A fasting blood sample was taken from each subject just before administration as baseline and a sample was obtained on the last day of the 12-week test period.

These two studies were approved by the institutional ethical committee according to the Helsinki Declaration.

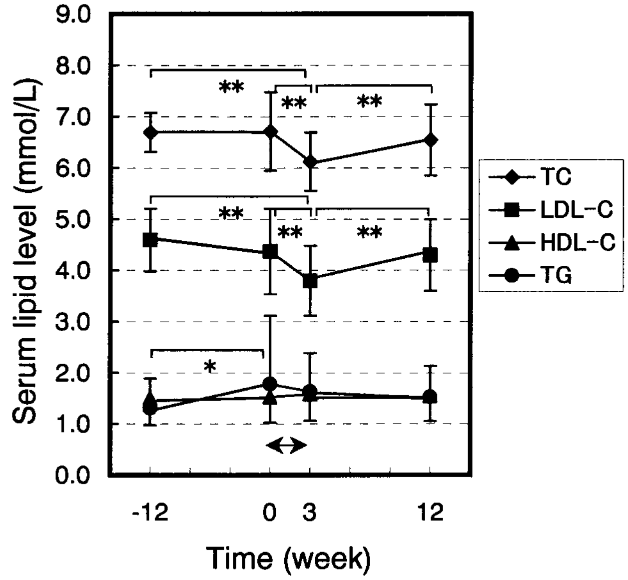

Figure 1. Serum lipid levels in patients who were administered two cans per day of the mixed green vegetable and fruit beverage for 3 weeks (study A): TC, total cholesterol; LDL-C, LDL cholesterol; HLD-C, HD cholesterol; TG, triglyceride. The serum lipid levels were measured at 12 weeks and just before administration, after 3 weeks of administration, and 9 weeks after the cessation of administration. Values shown are means ± SD, $n = 31$. An arrow (↔) shows the administration period. *, **: Significantly different by ANOVA and post-hoc comparison (Scheffe method) with $p < 0.05$ and $p < 0.01$, respectively.

Examination Categories and Method Used. In study A, a questionnaire was filled out by all study patients regarding food intake (*15*), exercise, sleeping patterns, and tobacco and alcohol consumption 1 week before administration and at the last week of the administration period. A physician conducted a medical examination on each patient at the time of the blood sampling, measuring weight and blood pressure. Clinical testing on the blood samples, including TC, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG), was carried out at Ikagaku Co. (Kyoto, Japan). The serum levels of TC, HDL-C, and TG were enzymatically assayed with commercially available kits, L-type Wako cholesterol (Wako Pure Chemical Industries Ltd., Osaka, Japan) (*16*), Determiner-L HDL-C (Kyowa Medex Co. Ltd., Tokyo, Japan) (*17*), and Auto L (Mizuho) TG-FR (Mizuho Medy Co. Ltd., Saga, Japan) (*18*), respectively. The serum LDL-C levels were calculated using the Friedewald formula (LDL-C = TC − HDL-C − TG/5) (*19*).

Statistical Analyses. Values are expressed as the means ± standard deviation (SD). A paired *t* test or an analysis of variance (ANOVA) and post-hoc comparison were conducted for the data, as appropriate. Statistical significance was considered at $p < 0.05$.

RESULTS

Figure 1 shows the change in serum lipid levels in study A. TC values significantly changed from 6.7 ± 0.8 mmol/L at baseline (0 week) to 6.1 ± 0.6 mmol/L (9% decrease) after 3 weeks of the administration of two cans of the test beverage per day, while LDL-C values significantly changed from 4.4 ± 0.8 to 3.8 ± 0.7 mmol/L (13% decrease). At 9 weeks after the cessation of the administration, TC levels increased to 6.5 ± 0.7 mmol/L and LDL-C levels also returned to 4.3 ± 0.7 mmol/L, which were not significantly different from the preadministration levels. No significant change was observed in the levels of HDL-C (from 1.5 ± 0.5 to 1.6 ± 0.5 mmol/L) and TG (from 1.8 ± 1.3 to 1.6 ± 0.8 mmol/L) during the course of the study.

Table 2. Body Weights, Body Mass Index, and Nutrient Intakes in Study A Patients before and during Administration Periods[a,b]

	before	during
body weight, kg	58.5 ± 11.2	58.5 ± 11.0
BMI[c]	22.1 ± 3.1	22.1 ± 3.0
energy, MJ	8.4 ± 3.1	7.7 ± 2.1
protein, g	69.9 ± 21.5	66.0 ± 18.9
fat, g	46.3 ± 14.0	41.8 ± 11.3
cholesterol, mg	231 ± 86	225 ± 74
nonfibrous carbohydrate, g	300 ± 148	273 ± 83
dietary fiber, g	9.2 ± 3.2	11.2 ± 3.3
potassium, g	1.7 ± 0.6	2.3 ± 0.6

[a] Values are means ± SD, $n = 31$. [b] Energy and nutrient intakes per day including the test beverage were calculated from 7-day food intake records at 1 week before administration (before) and at the last week of the administration period (during). [c] BMI, body mass index.

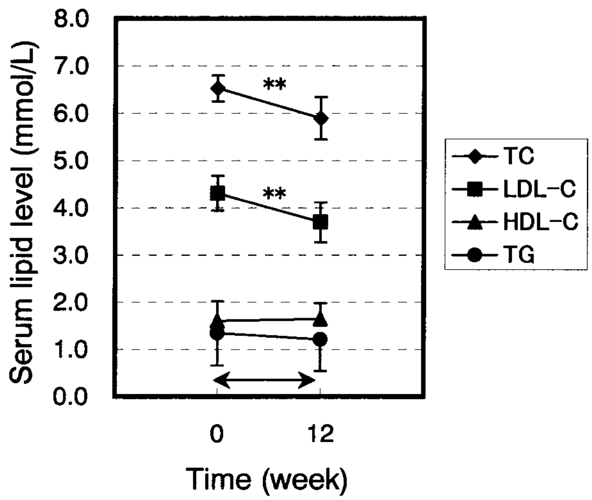

Figure 2. Serum lipid levels in patients who were administered one can per day of the mixed green vegetable and fruit beverage for 12 weeks (study B): TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TG, triglyceride. The serum lipid levels were measured just before administration and after 12 weeks of administration. Values shown are means ± SD, $n = 14$. An arrow (↔) shows the administration period. **: Significantly different by paired *t* test with $p < 0.01$.

Body weight, body mass index (BMI), and daily nutrient intakes including the test beverage before and during administration periods, determined using a questionnaire in study A, are shown in **Table 2**. There were no significant differences in body weight or BMI before versus during the administration periods. Examination of nutrient intakes showed significant increases in intakes of dietary fibers (∼2 g/day) and potassium (∼0.6 g/day) during the administration period. There were no significant differences in other nutrients.

Figure 2 shows the serum lipid levels before and after administration of one can of the test beverage per day for 12 weeks in study B. TC values changed significantly from 6.5 ± 0.3 to 5.9 ± 0.4 mmol/L after the administration (10% decrease), while LDL-C values changed significantly from 4.3 ± 0.4 to 3.7 ± 0.4 mmol/L (14% decrease). No significant change was observed for HDL-C (from 1.6 ± 0.4 to 1.7 ± 0.3 mmol/L) or TG (from 1.3 ± 0.7 to 1.2 ± 0.7 mmol/L).

In addition to serum lipids, blood laboratory tests before and after the study revealed no significant changes in the number of peripheral blood cells and biochemical values, as well as blood pressure, with all measurements being within normal ranges. No subjective symptoms or abnormal physical observations were witnessed at the conclusion of the study.

With regard to compliance measured by administration records, 71% of the subjects in studies A and B completely drank all of the assigned samples, and the rest of them forgot to drink at most 3 cans of the samples during the administration period. Ninety-seven percent of the assigned samples were drunk on the average. No patients dropped out during the test periods.

DISCUSSION

Vegetables, fruits, and their constituents are potent effectors of biological systems in humans (*5*). The cholesterol-lowering effects of vegetables, fruits, and their constituents have been examined in detail. Daily doses of these food agents that showed cholesterol-lowering effects in humans have been reported as follows: a variety of vegetables (570 g/day) and fresh apples (600 g/day), fresh carrots (200 g/day), apples (350−400 g/day), guava fruit (0.5−1 kg/day), garlic (10−20 g/day), and a low saturated fat diet combined with a vegetable (soy) protein (33 g/day) and a high soluble fiber (18 g/day) (*5*, *20*).

The U.S. Food and Drug Administration recommends including four servings of at least 6.25 g each (25 g/day) of soy protein into a diet low in saturated fat and cholesterol to reduce the risk of heart disease. A meta-analysis found that soy protein consumption achieved an average 9.3% decrease in TC and a 12.9% decrease in LDL-C (*21*).

In study A, we have concluded through a test on subjects with hypercholesterolemia that serum TC and LDL-C levels were significantly reduced (9 and 13%, respectively) by drinking two cans (320 g) of the mixed green vegetable and fruit beverage every day for 3 weeks. These lipid levels returned to baseline within 9 weeks after cessation of the administration of the test beverage. In study B, we have also shown that serum TC and LDL-C levels were significantly reduced (10 and 14%, respectively) by drinking 1 can (160 g) of the test beverage every day for 12 weeks. The reduction rates in TC and LDL-C levels by drinking the test beverage are almost equal to those by soy protein consumption described above.

The cholesterol responses to the two doses of the supplemental beverage tested in this study were similar. The similar clinical effects in these separate studies imply that the mechanism contributing to the hypocholesterolemic effect is saturable or the length of the intervention is contributing in part to the response.

On the other hand, there was no significant change in serum TG or HDL-C levels in either study. Thus, the serum lipid lowering effect of the test sample on TC level was due to that on the LDL-C level, leading to a decrease in the atherogenic index (TC/HDL-C ratio) (*22*−*24*).

It is not clear in this study which constituents in the mixed green vegetable and fruit beverage showed hypocholesterolemic action. Generally, the effects of vegetables and fruits on cholesterol metabolism are attributed to their fiber content. Isolated dietary fibers from these plants, such as pectins (12−50 g/day) (*25*−*27*), guar gum (10−20 g/day) (*6*, *28*, *29*), and psyllium (6−15 g/day) (*30*, *31*), have been shown to lower cholesterol levels in humans. The mechanisms for the cholesterol-lowering in humans remain unclear. Results from in vitro and animal studies that used isolated fibers suggested that the reductions in cholesterol are probably due to different mechanisms specific to each fiber source and to different dietary fiber intake amounts (*32*−*34*). Possible mechanisms include (1) increased fecal excretion of bile acids and neutral steroids, (2) altered ratios of primary to secondary bile acids, (3) increased fecal excretion of cholesterol and fatty acids, and (4) indirect effects, such as high-fiber foods replacing fat- and cholesterol-containing foods in a diet (*35*). However, the amount of dietary fiber (1.3−2.6 g/day) provided by the consumption of one or two cans of the test beverage is far out of proportion with the doses (6−50 g/day) of isolated dietary fibers described above to obtain a significant reduction in serum cholesterol levels in humans.

As other potent constituents in the test beverage, cabbage leaf proteins (*36*) and *S*-methylcysteine sulfoxide (SMCS) (*37*, *38*) have been shown to have cholesterol-lowering effects on animals. The total protein content in the beverage is 1 g/160 g. This protein amount seems to be far less than the daily dose of soy protein recommended for obtaining a significant reduction in serum cholesterol levels in humans. On the other hand, SMCS, a naturally occurring S-containing amino acid, is contained at high concentrations in *Brassica* vegetables such as broccoli and cabbage and *Allium* vegetables such as onion (*39*, *40*). The mechanism of SMCS for cholesterol-lowering effects has been hypothesized to enhance fecal bile acid excretion and cholesterol 7α-hydroxylase activity, the rate-limiting enzyme of bile acid biosynthesis, in the microsomal fraction of the liver (*37*, *38*). Indeed, the test beverage contained broccoli and cabbage as main materials, and the amount of SMCS derived from these *Brassica* vegetables in the beverage was at least 20 mg/160 g of juice.

Therefore, the dietary fibers and other potent constituents including SMCS in the beverage might have shown synergistic effects to lower cholesterol levels. Research on the contribution of these potent constituents is now being conducted.

In conclusion, we have shown for the first time that the canned mixed green vegetable and fruit beverage tested significantly lowered serum TC and LDL-C levels. This kind of sample made from natural products may become an alternative way to treat patients with hypercholesterolemia.

ABBREVIATIONS USED

LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; BMI, body mass index; SMCS, *S*-methylcysteine sulfoxide.

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