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흑차추출물의 체중 또는 체지방 감소 유효성 및 안전성 검증을 위한 무작위, 이중맹검, 위약대조 인체적용시험

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The Efficacy and Safety of Black Tea Extract on Weight or Body Fat Reduction in Overweight or Obese Subjects: A Randomized, Double-Blind, Placebo-Controlled Study

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Background: Black tea extracts (BTE), which are rich in gallic acid, have been associated with the improvement of obesity in rats. However, whether black tea consumption is beneficial in human subjects is unknown. In this study, we aimed to evaluate whether BTE can reduce body fat mass in human subjects.

Methods: We investigated the effects of BTE intake in 50 pre-obese and obese Korean adults (23 kg/m^2<body mass index <30 kg/m^2) in a randomized, double-blind, placebo-controlled study. Participants received 1 g of BTE or placebo once daily for 8 weeks. Effects of BTE were investigated using biochemical analyses and measurement of visceral fat content via computed tomography.

Results: After 8 weeks of BTE consumption the mean BMI decreased by 0.05±0.32 kg/m^2 in the BTE group compared with a decrease of 0.18±0.78 kg/m^2 in the placebo group. There was a 0.10±0.79 kg difference in weight within the BTE group. Abdominal computed tomography scans revealed a liver Hounsfield unit decrease of 0.32±5.84 in the BTE group compared with a decrease of 3.03±3.65 in the placebo group. None of the differences were statistically significant (P>0.05).

Conclusion: BTE was not effective in reducing human body weight or body fat composition, when compared with the effects of placebo.

Keywords: *Black Tea Extract; Obesity; Body Mass Index; Visceral Fat*

INTRODUCTION

The prevalence of obesity in both adults and children has increased dramatically, resulting in a world-wide health problem. Excess energy intake and reduced energy expenditure leads to abnormal and excessive accumulation of adipose tissue, which often results in development of obesity.[1)] Obesity is strongly associated with metabolic syndrome, which is characterized by insulin reisistance, hypertension, and hyperlipidemia.[2)]

While medications are available to aid in weight loss, increased interest has focused on functional and biologically active substances in foods and fermented foods.[3)] Among beverages, green tea has been extensively

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studied and reported to exhibit cholesterol-lowering and anti-oxidative effects, in addition to reducing abdominal fat. These effects can be attributed to catechins, such as epigallocatechin-3-gallate.[4] The underlying mechanism of the catechin-induced cholesterol-lowering effect is precipitation of mixed bile salt micelles.[5] Similarly, fermented Chinese black tea exhibited a similar precipitating effect on mixed bile salt micelles.[6] Chinese fermented black tea is processed by parching green tea leaves before fermentation with microorganisms, such as with *Aspergillus* species.

A preclinical toxicology study showed that administration of up to 2,000 mg/kg/day of fermented black tea extracts to rats for 2 weeks showed no toxicity.[3] In a separate study conducted over 8 weeks involving 20 subjects, subjects ingested 250 mg or 333 mg of black tea extract, which resulted in significant reduction in total cholesterol and low-density lipoprotein (LDL)-cholesterol levels without additional toxicity or adverse events.[7]

While many of the previous reports on black tea extracts (BTE) studied its effects on serum cholesterol levels, effects on body fat and obesity have not been evaluated. Uchiyama et al.[8] previously investigated the possiblity that black tea may prevent obesity and found that BTE may prevent diet-induced obesity by inhibiting intestinal lipid absorption. In our study, we evaluated the efficacy and saftety of BTE and its effects on weight and body fat reduction in overweight or obese subjects. Based on previous studies conducted on the effects of BTE, we performed a randomized, double-blind, placebo-controlled study using a 1 g/day dose of BTE in tablet form to test its effects on body weight and fat reduction.

METHODS

1. Black tea extract preparation

Black tea manufactured with leaves of *Camellia sinensis* L. in Yunnan Province, China, was purchased. Dried black tea (20 g) was extracted using 120 mL of 50% ethanol-water solution at 10°C–30°C for 72 hours. The filtered extracts were vacuum-evaporated at 45°C–60°C, then freeze dried to a tablet form. Using high-performance liquid chromatography, we determined the gallic acid concentration in the dried extract. Our BTE tablet contained 1.5% gallic acid.

2. Study design

This study was conducted from July, 2013 to March, 2014 on outpatients and was conducted in compliance with and following approval of the Institutional Review Board (IRB) (KC13HSSE0134).

Our clinical study was designed as an 8 week, randomized, double-blind, placebo-controlled study. Subjects deemed fit for this study were screened based on inclusion and exclusion criteria. The selected participants were then randomly placed into the test and control groups and were prescribed either BTE or placebo tablets for 8 weeks. All subjects were instructed to take 2 tablets twice a day (active ingredient 1 g/d).

Prior to beginning consumption of the tablets (day 1), all participants had their vital signs checked and underwent body composition analysis. In addition, the participants were given instructions on how to log their dietary intake in a diary, for up to 2 weeks prior to day 1 (visit 1). The final visit occurred after 8 weeks of tablet consumption (visit 5). Upon 8 weeks of ingesting the test tablets, participants returned to the outpatient department for a check of vital signs, symptoms and signs of adverse reactions, body composition analyses, and hematological and biochemical analyses.

3. Participants

Fifty subjects were placed in the intent-to-treat (ITT) group (25 test group, 25 placebo group) and 44 subjects were placed in the PP analysis group (22 test group, 22 placebo group) (Figure 1).

Inclusion criteria included men and women between the ages of 20 and 65 classified as over-weight or obese based on a body mass index (BMI) greater than 23 kg/m^2 but less than 30 kg/m^2. Subjects with active acute or chronic severe comorbidities including heart disease, kidney disease, liver disease, cerebrovascular disease, tuberculosis, rheumatic diseases, thyroid diseases, those diagnosed with secondary obesity due to Cushing's disease, diabetes mellitus, hypertension, those diagnosed with cancer within the last 5 years or those who have received chemotherapy within the last 5 years, history of having been on any pharmaceuticals affecting body weight (antidepressants, appetite suppressants), diuretics, oral contraceptives, steroids, and estrogens were excluded from the study. Pregnant or breast-feeding women were also excluded.

All subjects were asked to avoid taking any additional dietary supplements that could affect hypercholesterolemia, and to maintain their normal physical activity during the study period.

4. Study procedures

Each BTE tablet contained 500 mg of BTE and various bulking agents, including crystalline cellulose, hydroxypropyl methylcellulose, and magnesium stearate. The placebo tablets contained the same contents except

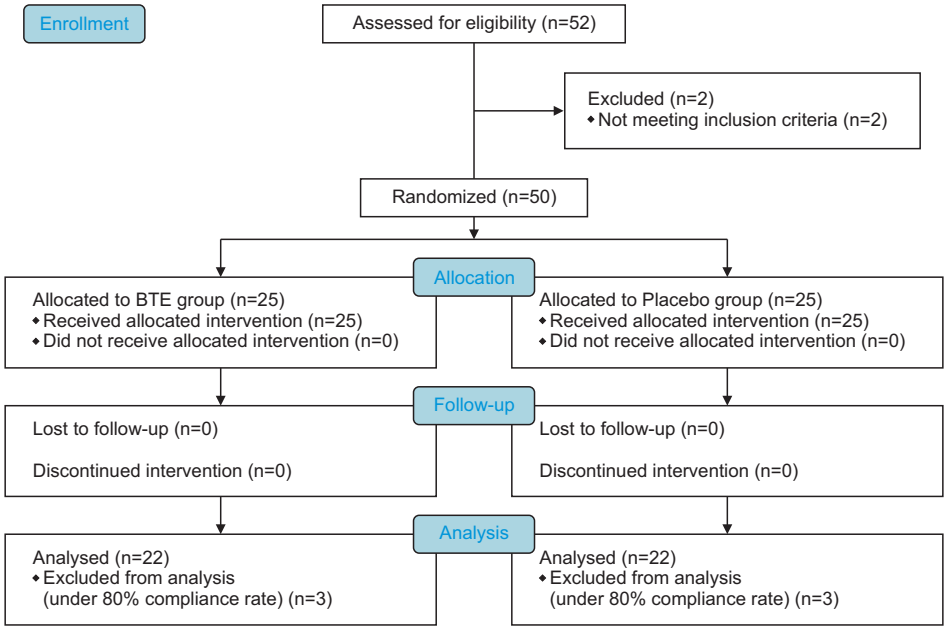

Figure 1. CONSORT Flow Diagram.
BTE, black tea extracts.

BTE.

Upon visits 1, 2, and 5, all participants were subjected to general physical examinations and laboratory blood tests. All clinically significant findings were recorded prior to day 1 and any adverse events associated with consumption of the tablets were also recorded.

Vital signs including blood pressure and pulse rate were recorded after 5 minutes of remaining in a seated position. Subjects' height and body weight were measured and BMI was calculated. Body fat, body fat ratio, and waist-hip ratio (WHR) were measured using the InBody H20N (InBody Venture Center, Seoul, Korea).

The following biochemical parameters were measured at a hematologic analysis laboratory: White and red blood cell counts, hemoglobin, hematocrit, platelet levels, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, total bilirubin, triglyceride, high density lipoprotein-cholesterol, LDL-cholesterol, total-cholesterol, and thyroid-stimulating hormone.

Computed tomography (CT) scans were performed to assess changes in intra-abdominal adipose tissues and subcutaneous abdominal tissue with weight loss.[9] These scans were performed using SOMATOM Definition AS+; SIEMENS, Seoul, Korea.

Liver CTs were taken at visits 2 and 5 to compare baseline liver Hounsfield unit (HU) and spleen HU to HU after 8 weeks of tablet consumption. The difference between liver and spleen attenuation values must be measured in order to establish the CT diagnosis of hepatic steatosis.[10] A region of interest (ROI) was recorded for both liver and spleen, and mean CT attenuation values (in Hounsfield units) were obtained.[11] Supine images were evaluated on a standard picture archiving and communication system as 5 mm thick sections reconstructed at 3 mm intervals. Mean CT attenuation values (in HU) of the three separate ROIs were scored and recorded for the liver and spleen using a validated single-slice standard region-of-interest method.[12] Care was taken to retrieve homogeneous sample areas representative of the parenchyma, while avoiding vessels, bile ducts, focal lesions, focal changes of fatty liver or fatty sparing, as well as the surface margins.[11]

By using the ratio of liver to spleen attenuation, i.e. using spleen as an internal control, possible confounding factors across images, such as the effect of obesity, could be reduced. Liver to spleen ratio was used as an index of liver fat content.[13] The following five unenhanced CT criteria for diagnosis of hepatic steatosis were applied: liver attenuation ≤40 HU, liver attenuation less than or equal to spleen attenuation minus 10 HU, liver attenuation less than or equal to spleen attenuation, liver attenuation less than or equal to spleen attenuation plus 5 HU, and liver-to-spleen attenuation ratio less than or equal to 1.1.[11]

5. Statistical analysis

For efficacy assessment, the main subjects of analyses were placed in the ITT set, and the subsidiary subjects of analyses were placed in the per-protocol (PP) set.[14] Safety assessment was done by using the ITT set

as the main subjects of analyses. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA). The ITT group consisted of 50 individuals and the PP group contained 44 individuals.

For baseline study, subject data from the ITT and PP sets including demographics, vital signs, somatometry, body composition, blood chemistry, and body fat percentage were obtained during subject screening (visit 1) and were compared using an independent t-test and Wilcoxon's rank sum test.

Efficacy assessment variables included BMI, body fat percentage, WHR, surface area of abdominal fat obtained from abdominal CT images, and fatty liver assessment obtained from liver CT images.

Safety of the BTE tablets were assessed using adverse reactions, physical examinations, vital signs, hematological tests, pregnancy test, and concomitant intake of other drugs as variables. A total of 50 participants who were randomized into the ITT group and met the selection/exclusion criteria were the subjects of analyses for safety evaluation.

Comparisons between the ITT and PP sets regarding these variables were done using an independent t-test, a paired t-test, Wilcoxon's rank sum, and signed rank tests.

RESULTS

Clinical characteristics and body composition parameters for the study group are presented in Table 1. The test group consisted of 5 males (20.00%) and 20 females (80.00%) The placebo group consisted of 4 males (16.00%) and 21 females (84.00%). The mean age of the test group was 43.72 years (range: 23–65 years) and the mean age of the placebo group was 46.56 years (range: 21–65 years). Baseline characteristics of the two groups were not significantly different (P>0.05).

Laboratory examinations were performed on all 50 subjects upon screening and the differences between the test group and placebo group were studied. There were no statistically significant differences between the two groups in any of the parameters compared (P>0.05) (Table 2).

The variables used as markers for efficacy of BTE were changes in BMI, body fat ratio, weight, abdominal fat, hepatic steatosis, and WHR (Table 3). When comparing baseline parameters to those after 8 weeks of taking either BTE or placebo tablets, there was a mean decrease in BMI of 0.05±0.32 kg/m^2 in the BTE group and a decrease of 0.18±0.78 kg/m^2 in the placebo group. Body fat ratio decreased by 0.22±1.04 kg in the BTE group and increased by 0.04±1.40 kg in the placebo group from the baseline till after the end of the 8 week study period. Weight in the BTE group and the placebo group decreased by 0.10±0.79 kg and 0.54±2.26 kg, respectively, from the baseline till after the end of the 8 week study period. The change in visceral fat at 8 weeks compared with the baseline was a reduction of 1.84±24.63 cm^2 and 6.25±18.93 cm^2 for the BTE group and placebo group, respectively. The changes between the two groups and the

Table 1. Baseline characteristics of the study group

Variable	BTE group	Placebo group	P-value
ITT, n	25	25	
Age (y)	43.72±11.61	46.56±11.12	0.3815*
Gender			
Men	5 (20.00)	4 (16.00)	
Women	20 (80.00)	21 (84.00)	1.0000†
Height (cm)	162.89±7.49	160±7.74	0.3158*
Weight (kg)	70.48±8.27	66.96±7.61	0.1236*
BMI (kg/m^2)	26.48±1.62	25.88±1.72	0.2074*
Pulse (beats/min)	71.84±3.83	72.32±3.99	0.3334‡
Blood pressure (mmHg)			
Systolic	115.20±11.59	110.40±10.52	0.0950‡
Diastolic	76.80±8.02	74.08±6.94	0.0545‡

Values are expressed as mean±standard deviation or number (%).
BTE, black tea extracts; ITT, intent-to-treat; BMI, body mass index.
*Independent t-test. †Fisher's exact test. ‡Wilcoxon's rank sum test.

Table 2. Laboratory results of the study group

Variable	BTE group (n=25)	Placebo group (n=25)	P-value
ITT, n	25	25	
WBC (10^9/L)	6.16±1.59	6.23±1.19	0.8712*
RBC (10^{12}/L)	4.57±0.38	4.43±0.28	0.1837†
Hemoglobin (g/dL)	13.83±1.48	13.61±0.94	0.3766†
Hematocrit (%)	40.90±3.70	39.92±2.58	0.1072†
Platelet (10^9/L)	256.72±62.26	253.72±47.60	0.9923†
BUN (mg/dL)	13.29±4.06	14.50±4.51	0.3227*
Creatinine (mg/dL)	0.79±0.14	0.74±0.15	0.1275†
Total bilirubin (mg/dL)	0.74±0.34	0.69±0.19	0.6764†
AST (SGOT) (U/L)	23.24±10.67	21.36±6.18	0.8230†
ALT (SGPT) (U/L)	23.52±13.18	21.16±7.17	0.9071†
γ-GTP (uU/dL)	25.12±29.25	31.32±31.32	0.1739†
TG (mg/dl)	144.04±88.68	119.48±103.85	0.0807†
HDL-cholesterol (mg/dL)	51.32±10.17	55.72±13.05	0.1900*
LDL-cholesterol (mg/dL)	119.72±32.20	119.44±33.10	0.9759*
Total-cholesterol (mg/dL)	196.44±43.43	201.60±40.23	0.6649*
TSH (U/L)	2.11±1.06	2.00±1.20	0.5346†

Values are expressed as mean±standard deviation.
BTE, black tea extracts; ITT, intent-to-treat; WBC, white blood cell; RBC, red blood cell; BUN, blood urea nitrogen; AST, aspartate aminotransferase; SGOT, serum glutamic-oxaloacetic transaminase; ALT, alanine aminotransferase; SGPT, serum glutamate-pyruvate transaminase; γ-GTP, γ-glutamyl transpeptidase; HDL, high density lipoprotein; LDL, low density lipoprotein; TSH, thyroid-stimulating hormone.
*Independent t-test. †Wilcoxon's rank sum test.

Table 3. Changes in evaluated values after 8 weeks in the ITT group

Variable		BTE group (n=25)	Placebo group (n=25)	P-value
BMI (kg/m^2)	Baseline	26.64±1.67	26.04±1.73	0.2244†
	At week 8	26.58±1.78	25.86±1.83	
	Difference*	-0.30±1.44	0.25±1.17	0.1412†
Body fat ratio (%)	Baseline	35.36 ±4.86	35.20±5.00	0.9177†
	At week 8	34.85±4.83	35.39±5.24	
	Difference*	-0.50±1.36	0.18±1.17	0.0801†
Weight (kg)	Baseline	70.84±8.38	67.38±7.53	0.1312†
	At week 8	70.74±8.56	66.85±6.75	
	Difference*	-0.10±0.79	-0.54±2.26	0.6978‡
Abdominal CT				
Surface area of visceral fat (cm^2)	Baseline	95.92±33.36	105.95±39.86	0.3320‡
	At week 8	94.08±29.61	99.70±33.12	
	Difference*	-1.84±24.63	-6.25±18.93	0.4810†
Surface area of subcutaneous fat (cm^2)	Baseline	251.44±63.59	227.87±60.17	0.0952‡
	At week 8	247.38±71.47	226.62±64.80	
	Difference*	-4.06±30.75	-1.24±22.74	0.7148†
Ratio of visceral fat/subcutaneous fat (cm^2)	Baseline	0.42±0.25	0.52±0.30	0.140‡
	At week 8	0.42±0.23	0.49±0.27	
	Difference*	0.00±0.17	-0.02±0.12	0.5139†
Liver CT				
Liver HU	Baseline	56.32±8.79	59.30±8.13	0.1508‡
	At week 8	56.00±9.55	56.27±8.69	
	Difference*	-0.32±5.84	-3.03±3.65	0.0557†
Spleen HU	Baseline	48.82±3.10	49.23±3.56	0.6675†
	At week 8	49.09±2.87	49.84±2.95	
	Difference*	0.27±3.56	0.61±3.45	0.7309†
Waist hip ratio	Baseline	0.90±0.03	0.89±0.04	0.7037†
	At week 8	0.90±0.05	0.89±0.04	
	Difference*	0.00±0.03	0.00±0.02	0.6235†

Values are expressed as mean±standard deviation.
ITT, intent-to-treat; BTE, black tea extracts; BMI, body mass index; CT, computed tomography; HU, Hounsfield unit.
*Difference between baseline and after 8 weeks. †Independent t-test. ‡Wilcoxon's rank sum test.

changes within the same groups after 8 weeks were not significantly different.

Evaluation of abdominal CT scans revealed a liver HU decrease of 0.32±5.84 HU in the BTE group and a decrease of 3.03±3.65 HU in the placebo group. While comparison of HU values between the baseline and post 8 week within the placebo group revealed a statistically significant change (P=0.0004), the change in HU between the BTE and placebo groups was not statistically significant. The change in mean spleen HU from baseline to after 8 weeks was an increase of 0.27±3.56 HU in the BTE group and an increase of 0.61±3.45 HU in the placebo group. The changes within each study group and between the two groups were not statistically significant.

There were no changes in WHR after 8 weeks of BTE or placebo consumption (0.00±0.03 and 0.00±0.02, respectively). There were no statistically significant changes in WHR within each group or between the two groups.

Safety of BTE tablets was assessed by evaluation of adverse events, vital signs, laboratory tests, and physical examinations. None of the 25 participants placed randomly into the BTE group showed any signs of adverse events. Of the 25 participants placed into the placebo group, 2 participants showed 2 separate adverse events. None of these events were related to the intake of the placebo tablets and were not significant enough to cause these participants to drop out of the clinical trial.

DISCUSSION

BTE did not reduce weight or body fat in obese or overweight individuals in this study. However, in two separate studies carried out by Fujita and Yamagami,[7] 1 g/day BTE significantly lowered total cholesterol and LDL-cholesterol levels in human subjects after 3 months of consumption

without eliciting any adverse effects in the first study, and reduced TG levels, body weight, and BMI without any adverse effects or toxicity after 4 months of intake in the second study.[3] Based on the duration of those studies, future studies should have a minimum duration of 12 weeks to evaluate the effects on body fat. While this study could not statistically show that black tea consumption lowered body fat ratio and body fat mass, the BTE group showed a tendency of lower body fat when compared with the placebo group. Based on our results and this trend, future studies with positive results may be expected.

Thus far, efficacy and safety of BTE have been more extensively studied in animals compared to humans. A study by Fujita and Yamagami,[3] showed that BTE lowered total cholesterol and LDL-cholesterol levels in borderline hypercholesterolemic subjects at a dose of 333 mg/meal or 1 g/day. BTE consumption of 1 g/day was confirmed safe in both that study and in our clinical trial. Although current cholesterol-lowering drugs, such as HMG-CoA reductase inhibitors (statins), are widely available, they are associated with side effects such as liver impairments,[15] myopathy,[16] and rhabdomyolysis.[17] Unlike fiber and plant sterols, which nonspecifically inhibit absorption of nutrients and fat-soluble vitamins, BTE selectively inhibits reabsorption of cholesterol without affecting fat-soluble vitamins.[18]

Tea is one of the most widely consumed beverages in the world and while green tea has been the most extensively studied for its health benefits, a study by Yoshino et al. showed that green tea and black tea infusions had similar antioxidant activities in rat liver homogenates. Yoshino et al.[19] suggested that theaflavin, present in black tea, possesses at least the same antioxidant potency as catechins present in green tea. In the only existing study on human subjects that evaluated the anti-obesity effects of BTE, Kubota et al.[9] found that BTE exhibited weight-reducing effects in pre-obese Japanese patients. This study found that visceral fat areas (cm^2) were significantly ($P<0.05$) lower in coronal navel section CT images of all patients who received BTE for 12 weeks, when compared with those who did not receive BTE treated. BTE dosed at 1 g/day reduced visceral fat area by more than 3 cm^2 in 10 subjects (72%) within a 12-week ingestion period.[9] Thus, a longer ingestion period, as well as a follow up after termination, might have yielded a different result in our study.

Our study had several limitations. First, study participants were all recruited from the outpatient department of a single tertiary hospital, limiting generalizability. Second, patients with BMI greater than 30 kg/m^2 were excluded. A study including patients with severe obesity (BMI >30 kg/m^2) could have yielded more obvious results. Third, the study sample size was relatively small and the duration of the test period was also relatively short. Fourth, because a region of interest method was used to determine liver HU, there was the possibility of subjective error in selection of liver parenchyma to be included in the study.

Finally, an important limitation was the fact that total physical activity, alcohol intake, and diet of the participants could not be controlled. Factors that can heavily affect weight and body weight composition were not accounted for in this study.[20] Since BTE maybe a useful dietary supplement as opposed to an actual pharmacologic agent, additional nutritional and physical exercise programs may be advisable to see more obvious effects.

In conclusion, BTE did not decrease weight or body fat compared to placebo. While previous studies on BTE examined effects on serum cholesterol levels, effects on body fat and obesity were less characterized. Uchiyama et al. previously investigated the possibility that black tea may prevent obesity and found that BTE may prevent diet-induced obesity by inhibiting intestinal lipid absorption.[8] We performed a randomized, double-blind, placebo-controlled study using 1 g/day of BTE tablets to test the efficacy and safety of BTE and its effects on body weight and fat reduction in overweight or obese subjects. Since BTE has been proven to lower total cholesterol and LDL-cholesterol levels, a more extensive, long-term study involving a larger subject population should be conducted to further evaluate its effects on body fat reduction.

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