Original Research

GreenSelect® Phytosome as an Adjunct to a Low-Calorie Diet for Treatment of Obesity: A Clinical Trial

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Abstract

A recently developed oral formulation in the form of coated tablets (Monoselect Camellia®) (MonCam) containing highly bioavailable green tea extract (GreenSelect® Phytosome) was tested in obese subjects (n=100) of both genders on a hypocaloric diet. Fifty subjects were assigned to the green tea extract plus hypocaloric diet, while the other 50 subjects followed the hypocaloric diet only. After 90 days of treatment, significant weight loss and decreased body mass index (BMI) were observed in the group taking the herbal extract (14-kg loss in the green tea group compared to a 5-kg loss in the diet-only group); waistline was reduced only in male subjects. Besides the effect on weight and BMI, biochemical parameters (LDL-, HDL-, and total cholesterol, triglycerides, growth hormone, insulin-like growth factor-1, insulin, and cortisol) were improved in both groups. Leptin, not tested in the diet-only group, was reduced in patients taking MonCam. Taking into consideration the high safety profile of the product and the total absence of adverse effects observed during and after the trial, MonCam appears to be a safe and effective tool for weight loss. *(Altern Med Rev* 2009;14(2):154-160)

Introduction

Recent clinical studies have demonstrated that catechin derivatives, mainly in gallate form obtained by extracting the aerial, unfermented parts of *Camellia sinensis* L. (green tea), can increase basal energy expenditure by as much as four percent after oral administration of the extract containing at least 270 mg of epigallocatechin gallate.[1] This thermogenic action has been investigated by several authors and demonstrates a weight loss effect.[1-3]

Green Tea Extract

Composition and Active Ingredients

The active ingredients in unfermented green tea leaves are polyphenolic structures belonging to the flavonol family. These flavonols, easily identified by high performance liquid chromatograph-mass spectrophotometry (HPLC-MS), are epigallocatechin, catechin, epigallocatechin-3-O-gallate (EGCG), gallocatechin-3-O-gallate, epigallo-3-O-methylgallate, and epicatechin-3-O-gallate. This group of compounds is commonly referred to as "green tea catechins."[4]

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Table 1. Weight Variation (Average ± SD) in Overweight Subjects after 45 and 90 Days of Treatment

n	Group	Weight (kg)		
		Baseline	45 Days	90 Days
50	A	95.086 ± 16.377	93.138 ± 15.977	90.490 ± 15.388
50	B	96.142 ± 18.012	90.128 ± 16.651	82.298 ± 15.326*
*p<0.001 for difference between baseline and day 90				

Group A: hypocaloric diet; Group B: hypocaloric diet and 150 mg MonCam twice daily

Table 2A. BMI Variation (%) after 90 Days of Treatment

Group	n	BMI (%)
A	30**	-5
B	30**	-12*
* p<0.001 day 90 compared to baseline **15 male and 15 female subjects per group		

Group A: hypocaloric diet; Group B: hypocaloric diet and 150 mg MonCam twice daily

Mechanisms of Action

From a pharmacological standpoint, EGCG has engendered the most interest, with many green tea extracts standardized to contain a certain percent of this catechin.[4] EGCG in its pure form is under investigation for its antiangiogenic, antimetastatic, and antiviral properties.[5] Other mechanisms of action associated with EGCG include antioxidant, 5-α-reductase inhibition,[6] and antibacterial activity (against *Helicobacter pylori*[7] and *Streptococcus mutans* responsible for tooth decay).[8]

Green Tea Catechins and Weight Loss

Most common natural and synthetic treatments for weight loss target calorie reduction (appetite suppressants, enzyme inhibitors, natural fibers, etc). Weight loss can also be achieved by increasing daily energy expenditure.[9-12] Substances such as EGCG are believed to increase caloric consumption by increasing thermogenesis.[13]

An increase in energy expenditure can be achieved by increasing physical activity through exercise. In theory there are other ways to increase energy expenditure. Thermogenesis, the production of body heat, is linked to oxidation of body fat and is controlled mainly by the sympathetic nervous system. The sympathetic nervous system uses biogenic amines such as the neurotransmitter norepinephrine (NE) and self-modulates by activating enzymes such as monoamine oxidase (MAO) or catechol-*O*-methyl transferase (COMT). These enzymes inactivate norepinephrine involved in the reduction of thermogenesis. Blocking these inhibitory enzymes favors NE's thermogenic role. MAO and COMT inhibition *in vivo* can be studied by determining the urinary excretion of NE, which is increased by enzyme inhibition.[14-17]

In 1999, Dulloo et al demonstrated in a controlled study that oral administration of 270 mg EGCG (in a standardized green tea extract) produced a four-percent increase in energy expenditure, a 3.4-percent reduction in respiratory quotient, a 35-percent increase in fat oxidation, and a 40-percent increase in urinary NE concentration compared to baseline.[1] These results are probably due to EGCG inhibition of the enzymes responsible for NE's catabolism. The effect of EGCG is supported by a recent human study showing COMT inhibition by EGCG.[10]

All gallate-catechins of green tea possess COMT-inhibitory activity; this activity is highest for EGCG and is evident at nM concentrations. EGCG is a non-competitive inhibitor with an IC_{50} of 70nM.[18,19]

Table 2B. Waistline Variation (% Change from Baseline) after 90 Days of Treatment

Group	Total subjects	WLa (%)	Male subjects	WLm (%)
A	50	-5	22	-7
B	50	-10	29	-14*

*p<0.001 at day 90 compared to baseline
(WLa = all subjects; WLm = male subjects)

Group A: hypocaloric diet; Group B: hypocaloric diet and 150 mg MonCam twice daily

Table 3. Plasma TC, BS, TT (%) at Baseline and after 90 Days of Treatment

n	Group	TC (%)	BS (%)	TT (%)
30**	A	-10	-8	-20
30**	B	-25*	-10	-33*

*p<0.001 for difference between baseline and day 90
**15 male and 15 female subjects per group

Group A: hypocaloric diet; Group B: hypocaloric diet and 150 mg MonCam twice daily

Absorption of Green Tea Catechins

Despite the large amount of pharmacological and clinical data on the effects of naturally occurring polyphenols on animal and human health, these molecules are poorly absorbed orally. Oral consumption of purified plant polyphenols is also typically poor.

Being complexed with phospholipids, whose polar heads react well with the polyphenol's hydroxy (OH) groups, leads to the formation of stable complexes called phytosomes that show increased bioavailability of the polyphenolic fraction after oral administration. Phytosomes are often at least 3-5 times more bioavailable measured by area under the curve (AUC) than the free form botanical.[20,21]

A clinical study compared the absorption of non-complexed green tea (GreenSelect®; standardized to contain 60% polyphenols; 40% EGCG) and green tea as a phytosome (GreenSelect® Phytosome). After oral administration of GreenSelect to healthy subjects (n=12), EGCG reached maximum concentration (C_{max}) of 0.8 µg/mL after two hours. After oral consumption of an equal dose of the same green tea extract complexed with phospholipids (Greenselect Phytosome) (n=12), C_{max} was 1.9 µg/mL after two hours. The AUC value for the phytosome was three times greater than free form green tea. Furthermore, following administration of non-complexed green tea, EGCG cannot be traced in plasma four hours after oral administration. On the contrary, after administration of the phytosome, the EGCG plasma values after four hours were superior to the C_{max} of the free form at two hours (C_{max}=0.8 µg/mL).[22]

Materials and Methods

Monoselect Camellia® (MonCam) (150-mg tablets) containing GreenSelect Phytosome (Indena; Milan, Italy) was used for the study. The product was developed by Velleja Research (Pontenure, Piacenza, Italy) and manufactured by SIIT (Trezzano S/N, Milan, Italy).

In a multicenter clinical trial, MonCam was studied on 100 overweight subjects (20- to 40-percent over ideal weight; 44 women and 56 men, ages 25-60). Subjects were randomly divided into two groups (A and B) of 50 subjects each. The subjects were enrolled by the Clinic of Allergology and Clinical Immunology (Rome, Italy), the Centro Polispecialistico di Ricerca (Rome, Italy), and the Terme di Fontecchio, Citta' di Castello (Perugia, Italy) between June 2007 and February 2008.

Table 4. Plasma LDL, HDL, GH Percentage Change between Baseline and Day 90

n	Group	LDL (%)	HDL (%)	GH (%)
10	A	-9.33	+10	+20
10	B	-20.45	+21.43	+321**

**p<0.001 for difference between baseline and day 90

Group A: hypocaloric diet; Group B: hypocaloric diet and 150 mg MonCam twice daily

Table 5. Percentage Differences between Baseline and Day 90 for Plasma IGF-1, Insulin, and Cortisol

n	Group	IGF-1 (%)	Insulin (%)	Cortisol (%)
10	A	+14.79	-16.77	-13.33
10	B	+24.29*	-36.84*	-23.68*

*p<0.05 for difference between baseline and day 90

Group A: hypocaloric diet; Group B: hypocaloric diet and 150 mg MonCam twice daily

Group A followed a balanced hypocaloric diet (about 1,850 and 1,350 calories daily for men and women, respectively). In addition to the same hypocaloric diet, subjects in group B received 150 mg MonCam twice daily.

At the beginning of the study, group A (23 women, 27 men) presented an average weight of 95.1 kg (standard deviation [SD] ± 16.38), while group B (21 women, 29 men) presented an average weight of 96.1 kg (SD ± 18.01). The high SD is partially due to both groups being composed of male and female subpopulations with significantly different average weights. At enrollment, the weight range for men and women was 80-120 kg and 60-100 kg, respectively. Thus, the weight variation was ample even within the same gender groupings, also contributing to the relatively high SD. Another factor contributing to the high SD was that the initial absolute weight was not considered a selection criterion; rather, subjects were selected whose weight was considerably different from optimal weight. This clinical design allows for more realistic data collection and represents a Gaussian distribution of weights in an obese population.

The protocol, approved by the Territory Ethics Committee, was meant to establish the effectiveness of MonCam plus a low-calorie diet compared to a low-caloric diet alone for weight loss.

Body weight was measured on subjects at baseline and after 45 and 90 days of treatment. Other parameters measured at baseline and after 90 days include body mass index (BMI; 30 subjects/per group), waistline (WL; 50 subjects/group), total cholesterol (TC; 30 subjects/group), fasting blood sugar (BS; 30 subjects/group), and total triglycerides (TT; 30 subjects/group). LDL-cholesterol, HDL-cholesterol, growth hormone (GH), insulin-like growth factor-1 (IGF-1), insulin, cortisol, and leptin were analyzed at baseline and after 90 days in 10 subjects/group (body weight 90-150 kg; BMI 28-36; selected to avoid wide SD).

Study exclusion criteria included age < 25 or > 60, diabetes, history of a myocardial infarction in the past two years, endocrine-associated obesity, thyroid pathology, pregnancy or breastfeeding, severe hypertension, use of sex hormones (except oral contraceptives for which the doses remained unchanged), and failure to sign the informed consent form.

Regarding statistical analysis, the raw data was analyzed using "Graph Pad Software" and the unpaired *t* test results provided. Statistical analysis comparing percentage values was done by the Mann-Whitney *U* test.

Results

Group A (diet-only group) had an average body weight of 95.086 kg at baseline, 93.138 kg at 45 days, and 90.49 kg at 90 days. Group B (MonCam-plus-diet group) had an average weight of 96.142 kg at baseline, 90.128 kg at 45 days, and 82.298 kg at 90 days (Table 1).

Table 6. Plasma Leptin (mmol/L) in 10 Subjects from Group B (Hypocaloric Diet plus MonCam) Measured at Baseline and 90 Days

Patient	Gender	Baseline Weight(kg)	Weight (90 days) (kg)	Leptin (t=0)	Leptin (t=90)
SE	M	94.0	80.2	0.25	0.10
GG	M	100.0	83.7	0.23	0.12
PF	M	103.0	87.2	0.64	0.21
RT	M	98.5	84.6	0.61	0.15
SD	M	101.4	83.5	0.45	0.23
FD	M	103.1	86.5	0.62	0.37
SL	F	96.0	87.1	0.95	0.20
RB	F	101.0	87.4	1.05	0.90
MS	F	99.0	83.6	0.43	0.10
IR	F	95.2	84.2	0.91	0.37

Although analysis indicated statistically non-significant differences between the weight of the two groups at baseline and after 45 days, a significant decrease in body weight of group B was evident at 90 days compared to baseline.

Tables 2A and 2B indicate that BMI and WL were not significantly altered in group A at 90 days compared to baseline. On the other hand, BMI was significantly reduced by 12 percent and WL non-significantly reduced by 10 percent in group B at 90 days compared to baseline.

The male subpopulation in group B experienced a statistically significant 14-percent decrease in waist circumference on day 90 relative to baseline (WLm; Table 2B).

The difference between WLa (all subjects) and WLm (male subjects) can be attributed to the different anatomical distribution of the fat mass. It is more likely for fat to be localized predominantly in the abdominal area in obese male subjects compared to obese female subjects.

Measurements of total cholesterol, fasting blood sugar, and total triglycerides (Table 3) were made on 30 subjects per group, equally subdivided between men and women: TC, BS, and TT were decreased 10-, 8-, and 20 percent, respectively, in group A, and 25-, 10-, and 33 percent, respectively, in Group B. The decrease in TC and TT of Group B was statistically significant at 90 days compared to baseline levels.

At days 0 and 90, 10 subjects in each group were selected on the basis of body weight (90-105 kg) and BMI (28-36) for plasma analysis of LDL- and HDL-cholesterol, GH, IGF-1, insulin, and cortisol (Tables 4 and 5).

Group A (hypocaloric diet) demonstrated a reduction in LDL (from 130 ± 21 mg/L to 118 ± 22), an increase in HDL (from 40 ± 5 mg/L to 44 ± 7), an increase in GH (from 4.0 ± 2.2 µg/L to 4.8 ± 3.1), an increase in IGF-1 (from 142 ± 28 µg/L to 163 ± 35), a decrease in insulin (from 18 ± 2 mU/L to 15 ± 3), and a decrease in cortisol (from 150 ± 30 µg/L to 130 ± 15).

Group B (hypocaloric diet plus MonCam) demonstrated a reduction in LDL (from 132 ± 25 mg/L to 105 ± 15), an increase in HDL (from 42 ± 6 mg/L to 51 ± 7), an increase in GH (from 3.8 ± 1.5 µg/L to 12.2 ± 4.1), an increase in IGF-1 (from 140 ± 25 µg/L to 174 ± 28), a decrease in insulin (from 19 ± 3 mU/L to 12 ± 5) and a decreased cortisol (from 152 ± 37 µg/L to 116 ± 25). These results, although demonstrating a trend toward greater improvement in

group B compared to group A, were not statistically significant, probably due to the small sample size. Only the increase in GH was found to be statistically significant when comparing the two groups.

As shown in Table 6, subjects given MonCam (n=10) demonstrated a downward trend in leptin. Leptin values, determined according to Abdullah et al,[23] in 10 subjects from group B were lower after 90 days than at baseline. Although these data are preliminary, characterized by a small sample size and lack of controls, a possible relationship between weight loss and plasma leptin reduction is indicated.

Conclusions

The study's objective was to clinically evaluate the effect of MonCam (a preparation containing a standardized green tea extract complexed with phospholipids) plus a hypocaloric diet compared to a hypocaloric diet alone for weight loss, changes in BMI, and lab values associated with obesity. Oral consumption of 150 mg MonCam twice daily along with a hypocaloric diet resulted in significant weight loss after 90 days (14 kg) compared to the diet-only group (5 kg).

Other potential variables between groups should be considered; for example, it is possible that individuals given an oral treatment targeted to enhance weight loss might have followed the diet more strictly. However, all subjects were asked to keep a daily diet record (90% complied), and records show equally strict observance of the criteria for both groups.

The subjects in group B demonstrated greater improvement in BMI (12 percent compared to five percent in the diet-only group). Furthermore, male subjects treated with MonCam showed a 14-percent waistline reduction compared to a seven-percent reduction in the diet-only subjects. This latter result was obtained by examining the male subgroup only; waistline reduction in the entire population was not statistically significant. This difference is hypothesized to be due to different fat mass distribution in male and female subjects. In males, fat mass is mainly distributed in the abdominal region, rendering the waistline highly affected by weight loss. In females, fat mass is often localized in the hips and thighs; therefore, weight loss is not as likely to cause a reduction in waist circumference.

Diet-plus-MonCam positively influenced lipid profiles as demonstrated by plasma total cholesterol and triglycerides. Results relevant to weight loss were also obtained when comparing LDL, HDL, GH, IGF-1, insulin, and cortisol levels in both groups. The most dramatic differences were noted in growth hormone. Group B demonstrated more than a three-fold increase (321% increase) from baseline, compared to a 20-percent increase in group A.

Although lacking in control values, plasma leptin in group B decreased between baseline and day 90, demonstrating a possible relationship with weight loss. In the 10 subjects analyzed, leptin decreased, up to 70-80 percent in a few cases. Because leptin was not measured in group A, it is impossible to know how much of the effect was from diet compared to green tea.

Considering the high safety profile (oral LD_{50} >4,000 mg/kg; no toxicity in sub-chronic and chronic toxicological investigations; Indena S.p.A., Milan, Italy; internal file) of the active ingredient (Greenselect Phytosome) used in the formulation and the absence of relevant side effects in treated subjects compared to untreated subjects, the product can be considered a safe and effective tool for weight loss and impacting obesity-related risk factors.

Additional studies are needed to determine whether the product demonstrates an anti-obesity effect without the hypocaloric diet. Moreover, the mechanism of action of the formulation's effect on lipid profiles, leptin, and other biochemical markers linked to obesity needs to be investigated.

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