# Cholesterol-Lowering Effect of a Theaflavin-Enriched Green Tea Extract

## *A Randomized Controlled Trial*

*David J. Maron, MD; Guo Ping Lu, MD; Nai Sheng Cai, MD; Zong Gui Wu, MD; Yue Hua Li, MD; Hui Chen, MD; Jian Qiu Zhu, MD; Xue Juan Jin, MS; Bert C. Wouters, MA; Jian Zhao, PhD*

**Background:** Tea consumption has been associated with decreased cardiovascular risk, but potential mechanisms of benefit are ill-defined. While epidemiologic studies suggest that drinking multiple cups of tea per day lowers low-density lipoprotein cholesterol (LDL-C), previous trials of tea drinking and administration of green tea extract have failed to show any impact on lipids and lipoproteins in humans. Our objective was to study the impact of a theaflavin-enriched green tea extract on the lipids and lipoproteins of subjects with mild to moderate hypercholesterolemia.

**Methods:** Double-blind, randomized, placebo-controlled, parallel-group trial set in outpatient clinics in 6 urban hospitals in China. A total of 240 men and women 18 years or older on a low-fat diet with mild to moderate hypercholesterolemia were randomly assigned to receive a daily capsule containing theaflavin-enriched green tea extract (375 mg) or placebo for 12 weeks. Main outcome measures were mean percentage changes in total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels compared with baseline.

**Results:** After 12 weeks, the mean ± SEM changes from baseline in total cholesterol, LDL-C, HDL-C, and triglyceride levels were −11.3% ± 0.9% ($P$ = .01), −16.4% ± 1.1% ($P$ = .01), 2.3% ± 2.1% ($P$ = .27), and 2.6% ± 3.5% ($P$ = .47), respectively, in the tea extract group. The mean levels of total cholesterol, LDL-C, HDL-C, and triglycerides did not change significantly in the placebo group. No significant adverse events were observed.

**Conclusion:** The theaflavin-enriched green tea extract we studied is an effective adjunct to a low-saturated-fat diet to reduce LDL-C in hypercholesterolemic adults and is well tolerated.

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*From the Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tenn (Dr Maron); Rui Jin Hospital, Shanghai, China (Dr Lu); Zhong Shan Hospital, Shanghai (Dr Cai and Ms Jin); Chang Zheng Hospital, Shanghai (Dr Wu); Xin Hua Hospital, Shanghai (Dr Li); Heart and Lung Hospital, Shanghai (Dr Chen); First Hospital, Wuxi, China (Dr Zhu); Nashai Biotech LLC, Nashville (Mr Wouters and Dr Zhao).*

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TEA, THE most widely consumed beverage in the world other than water,[1] has been associated with lower cardiovascular disease risk.[2-9] One proposed mechanism by which tea may protect from cardiovascular disease is a beneficial effect on lipids and lipoproteins. Several epidemiological studies have demonstrated an inverse relationship between tea consumption and cholesterol,[10-14] but a causal relationship has not been established.

It is biologically plausible that tea can lower cholesterol in humans. Both green and black teas are produced from the leaves of *Camellia sinensis*. Green tea is a rich source of polyphenols known as flavonoids. The predominant flavonoids in green tea are catechins. Theaflavins are polyphenol pigments present in black tea, formed from the polymerization of catechins during fermentation of green tea to form black tea.[1] Green and black teas,[15-18] green tea catechins,[19,20] and black tea polyphenols[21] lower plasma cholesterol in animal models of hypercholesterolemia. Green tea catechins have also been shown in rodents to decrease the solubility of cholesterol in micelles, thereby reducing intestinal cholesterol absorption.[22] Other animal studies show that green tea catechins reduce hepatic cholesterol content[19,23] and increase fecal excretion of total fatty acids, neutral sterols, and acidic sterols.[19,20] Black tea polyphenols also increase fecal excretion of total lipids and cholesterol in rodents.[21] Incubating human HepG2 liver cells in culture with green tea catechins increases low-density lipoprotein (LDL) receptor protein and binding activity,[24] apparently in response to decreased intracellular cholesterol concentration.

Despite the evidence from epidemiological and animal studies, several small, short-term controlled experiments in humans have found no lipid-lowering effects from green or black tea drinking.[25-29] One of these studies also tested capsules of green tea extract that did not



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include theaflavins, and the extract also failed to show any significant impact on lipids and lipoproteins.[25]

Because of the hypolipidemic effect of black tea polyphenols in animal studies and the lack of effect of a theaflavin-free extract in humans, we hypothesized that a tea extract containing both black tea theaflavins and green tea catechins might have a favorable impact on the lipid profile of patients with high cholesterol. To test this hypothesis, we performed a randomized, placebo-controlled parallel study of a green tea extract enriched with theaflavins in capsule form on the lipids and lipoproteins of individuals with mild to moderate hypercholesterolemia consuming a low-fat diet. The main outcome measures were the percentage changes in total cholesterol, LDL-cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels compared with baseline.

## METHODS

### PATIENTS

Patients 18 years and older with mild to moderate hypercholesterolemia (LDL-C, 130-190 mg/dL [3.4-4.9 mmol/L]) on a low-fat diet were recruited from outpatient clinics in 6 urban hospitals in China. Patients were excluded if their baseline triglyceride level was 350 mg/dL or greater (≥4.0 mmol/L); if they had uncontrolled hypertension (≥160/95 mm Hg), active pulmonary, hematologic, hepatic, gastrointestinal or renal disease, premalignant or malignant disease, diabetes, thyroid dysfunction, a history of coronary heart disease or other atherosclerotic disease, or any pathological values among routine clinical chemistry or hematological parameters; or if they consumed greater than 32% of daily energy from fat or had a body mass index of 35 or higher (calculated as weight in kilograms divided by the square of height in meters). Subjects were also excluded if they were taking any lipid-lowering medications or drugs that might interfere with lipid metabolism or taking cardiac or other vasoactive medications including antihypertensive drugs, thyroid hormones, oral contraceptives, cyclic hormone replacement therapy, dietary supplements (eg, fish oils, niacin at doses >400 mg/d, or dietary fiber supplements), or antioxidants, and they were prohibited from taking these medications during the course of the study. Patients were required to maintain a stable diet and level of physical activity during the 12-week intervention. Subjects were required to sign an informed consent to participate in the trial. The protocol was approved by the ethics committees in the 6 participating hospitals in accordance with the guidelines of the Declaration of Helsinki.

### STUDY DESIGN AND INTERVENTION

The study was a double-blind, randomized, placebo-controlled, parallel-group trial. Subjects were recruited from April 15, 2001, to July 19, 2001. Two weeks after signing an informed consent, those who met entry criteria were randomized to receive either a capsule containing a theaflavin-enriched green tea extract (Nashai Biotech, LLC, Nashville, Tenn) or placebo. Each active study capsule contained 75 mg of theaflavins, 150 mg of green tea catechins, and 150 mg of other tea polyphenols. The extract was manufactured according to good manufacturing practice guidelines,[30,31] with audits performed by a senior manager of a major pharmaceutical company. The extract was produced from raw *Camellia sinensis* leaves through a controlled fermentation process in which catechins are dimerized to form theaflavins. The placebo capsules were made from inert ingredients and were identical to the active capsules in weight, appearance, and odor.

Randomization was stratified by hospital. After randomization, subjects received either the tea extract capsule or placebo in a double-blind fashion and were instructed to take 1 capsule each morning for 12 weeks. After the randomization visit, clinic visits were scheduled in the morning of weeks 4, 8, and 12 after a 12-hour fast. Body weight was measured at each visit. Subjects were asked to record study capsules taken, concomitant medications, and any adverse events in subject diaries. Study capsules were dispensed at baseline, week 4, and week 8. The period of intervention was from June 7, 2001, to October 18, 2001.

#### Food Records

Subjects were asked to maintain their habitual, traditional Chinese diet, including their customary intake of tea. Nutrient intake was assessed using 3-day food records. A registered dietitian instructed subjects how to complete these records, and they were collected prior to baseline and after 8 weeks of treatment.

#### Lipid and Lipoprotein Analysis

Lipid and lipoprotein concentrations were measured at week –2, week 0, week 4, and week 12 after a 12-hour fast. Lipids and lipoproteins were analyzed enzymatically using standard laboratory procedures. Low-density lipoprotein cholesterol concentrations were calculated according to the method of Friedewald et al.[32] Prior to the trial, 40 reference samples were allocated to each participating hospital to perform quality validation. These samples represented 4 concentrations of LDL-C: low, medium low, medium high, and high. Measurement of the samples demonstrated tightly clustered test results, confirming high intrahospital and interhospital reliability of testing and standardization of testing among the 6 hospitals. The intrahospital coefficients of variation for measurement of total cholesterol and LDL-C were 1.9% or less and 4.1% or less, respectively. The interhospital coefficients of variation for measurement of total cholesterol and LDL-C were 2.0% and 1.0%, respectively. Throughout the study, to achieve uniform quality control among the 6 hospitals, 2 different reference standards for each hospital were tested daily.

#### Safety Monitoring

Serum chemistry tests were performed at baseline and at weeks 4 and 12 to monitor for safety. These tests included assessments of glucose, creatinine, uric acid, aspartate aminotransferase, total bilirubin, albumin, globulin, sodium, chloride, serum urea nitrogen, calcium, lactate dehydrogenase, alkaline phosphatase, total protein, albumin-globulin ratio, potassium, gamma-glutamyltransferase, and phosphorus. A complete blood count with an automated differential was performed at baseline and week 12.

### STATISTICAL ANALYSIS

Changes in lipoprotein concentrations at weeks 4 and 12 were analyzed in comparison with concentrations at week 0. Statistical analysis was performed using the SAS 6.12 (SAS Institute Inc, Cary, NC). Approximately 100 subjects per treatment group were required to achieve 80% power to detect a treatment difference of at least 0.15. This calculation is based on the assumption that the true treatment difference is at least 0.20 and the SD is 0.11.



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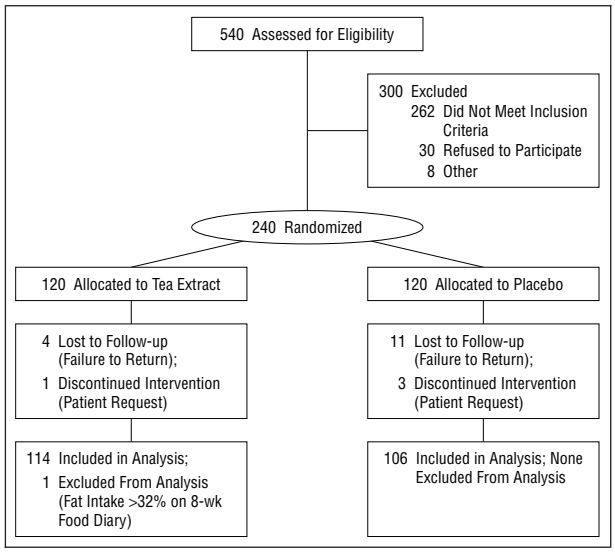


**Figure 1.** Flowchart of trial participants.

Statistical analysis of the efficacy of the intervention was performed on all randomized subjects who had a baseline evaluation, at least 1 on-therapy evaluation, and no deviation from the study protocol. The efficacy analysis was based on the percentage change from baseline for total cholesterol, LDL-C, HDL-C, and triglyceride levels. Between-group comparisons were performed using analysis of covariance. Baseline characteristics of the 2 groups were compared by use of the $\chi^2$ test for categorical variables and 2-tailed unpaired *t* test.

Evaluation of treatment safety, such as adverse events and abnormal findings from clinical laboratory tests, was performed using $\chi^2$ or the Fisher exact test. Analysis of covariance was used to assess laboratory safety monitoring test parameters, using treatment as the main factor and baseline value as the covariate. All statistical tests on safety data were performed using 2-sided tests of significance with a maximal critical $\alpha$ level of .05. Data are expressed as the mean with confidence intervals when applicable.

## RESULTS

The present study comprised 240 randomized subjects, and 220 subjects completed the trial (**Figure 1**). The baseline characteristics are presented in **Table 1**. All subjects were Asian. Of subjects in the treatment and placebo groups, 95% and 88%, respectively, finished the study. Compliance with the study capsule was 99.6% in the treatment group and 99.9% in the placebo group. No subject in either group had a capsule intake of less than 80%.

### FOOD RECORDS AND BODY MASS INDEX

Evaluation of the 3-day food diaries showed that both groups consumed a low-fat diet at baseline and at 8 weeks (**Table 2**). There were statistically significant increases in percentage of calories from protein, decreases in percentage of calories from total and polyunsaturated fat, and increases in cholesterol intake from baseline to week 8. In addition, there was an increase in total energy consumption in both groups, and this reached statistical significance in the placebo group. No statistical difference was observed for nutrient intake between the intervention and placebo groups at baseline or at 8 weeks for any of the dietary variables. Approximately half of the subjects in both groups consumed tea on a regular basis, with most subjects drinking 1 to 4 cups per day. At 8 weeks, subjects reported no changes in their tea-drinking habits compared with baseline. There were no statistically significant changes in body mass index in either group during the study (data not shown).

**Table 1. Baseline Characteristics of Subjects in the Tea Extract and Placebo Groups***

| Characteristic | Tea Extract | Placebo |
|---|---|---|
| No. of patients | 120 | 120 |
| Age, y | 54.4 ± 9.3 | 55.0 ± 11.7 |
| Sex | | |
| Male | 53 (44.2) | 47 (39.2) |
| Female | 67 (55.8) | 73 (60.8) |
| Body mass index† | 24.0 ± 2.8 | 24.4 ± 2.6 |
| Cigarette smokers | 26 (21.7) | 19 (15.8) |
| Dietary fat intake, % | 22.9 ± 4.8 | 23.0 ± 5.3 |
| Total cholesterol, mg/dL | 244 ± 22 | 239 ± 25 |
| LDL-C, mg/dL | 159 ± 17 | 155 ± 18 |
| HDL-C, mg/dL | 55 ± 12 | 55 ± 15 |
| Triglycerides, mg/dL | 189 ± 78 | 175 ± 75 |

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert lipoprotein levels to millimoles per liter, multiply by 0.0259 for cholesterol and 0.0113 for triglycerides.

*Data are mean ± SD or number (percentage) unless otherwise specified. Differences between the groups were not significant for any of the baseline variables.

†Calculated as weight in kilograms divided by the square of height in meters.

### LIPID AND LIPOPROTEIN RESULTS

There were no significant differences in baseline lipid and lipoprotein values between groups. Mean percentage changes in lipid parameters from baseline to week 12 are presented in **Figure 2**. In the treatment group, after 4 weeks of intervention, total cholesterol decreased by 6.7%±0.8% and LDL-C decreased by 9.6%±1.1%; after 12 weeks, total cholesterol decreased by 11.3%±0.9% ($P<.01$) and LDL-C decreased by 16.4%±1.1% ($P<.01$). There were no significant changes in total cholesterol or LDL-C in the placebo group during the study. After 12 weeks, HDL-C rose 2.3%±2.1% ($P=.27$) and triglycerides rose 2.6%±3.5% ($P=.47$) in the tea extract group. In the placebo group, HDL-C fell 0.7%±1.6% ($P=.67$) and triglycerides rose 5.6%±3.8% ($P=.14$). The mean total cholesterol to HDL-C ratio fell from 4.61±1.03 to 4.05±0.91 ($P<.001$) from baseline to 12 weeks in the tea extract group, but did not change significantly in the placebo group (from 4.55±1.22 to 4.57±1.18; $P=.85$).

We attempted to identify any differential LDL-C–lowering effect of the tea extract according to habitual tea consumption or baseline LDL-C concentration, but found none. Among subjects randomized to the tea extract, LDL-C fell 16.5%±1.6% in those who did not drink tea compared with a 17.3%±1.8% reduction in subjects who drank 1 to 4 cups per day ($P=.73$ for comparison with nondrinkers) and a 13.5%±3.2% reduction in those who drank 5 to



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**Table 2. Average Daily Nutrient Intake as Assessed by 3-Day Food Records at Baseline and 8 Weeks***

| Characteristic | Placebo Group | | | Tea Extract Group | | |
|---|---|---|---|---|---|---|
| | Week 0 | Week 8 | *P* Value | Week 0 | Week 8 | *P* Value |
| Total energy, kcal/kg | 26.6 ± 7.0 | 28.6 ± 6.6 | .005 | 27.0 ± 7.4 | 27.9 ± 6.3 | .24 |
| Protein, % | 18.4 ± 2.9 | 20.9 ± 3.47 | <.001 | 18.0 ± 3.6 | 20.1 ± 3.5 | <.001 |
| Carbohydrates, % | 58.3 ± 6.34 | 57.4 ± 5.8 | .73 | 59.0 ± 6.2 | 58.8 ± 6.2 | .22 |
| Total fat, % | 23.2 ± 5.1 | 21.8 ± 4.3 | .003 | 23.0 ± 4.7 | 21.1 ± 4.9 | .02 |
| Saturated fat, % | 5.9 ± 1.6 | 6.1 ± 1.7 | .20 | 5.9 ± 1.6 | 5.7 ± 1.8 | .37 |
| Polyunsaturated fat, % | 6.8 ± 1.9 | 5.8 ± 1.9 | <.001 | 6.8 ± 2.0 | 5.6 ± 2.0 | <.001 |
| Cholesterol, mg/dL | 418 ± 183 | 484 ± 201 | <.001 | 395 ± 188 | 511 ± 222 | .005 |
| Tea consumption, No. | | | | | | |
| Drinking/no drinking | 56/50 | 56/50 | . . . | 60/54 | 60/54 | . . . |
| 1-4 Cups/d | 38 | 38 | . . . | 46 | 46 | . . . |
| 5-10 Cups/d | 17 | 17 | . . . | 14 | 14 | . . . |
| >10 Cups/d | 1 | 1 | . . . | 0 | 0 | . . . |

SI conversion factor: To convert cholesterol to millimoles per liter, multiply by 0.0259.
*Data are mean ± SD unless otherwise specified. Macronutrients are presented as percentage of total energy intake. There were no statistically significant differences between groups at baseline or 8 weeks. There were no significant differences between the 2 groups in tea consumption at baseline.

10 cups per day (*P*=.39 for comparison with nondrinkers). Subjects in the active treatment group with baseline LDL-C in the upper half of the study sample (160-190 mg/dL [4.14-4.91 mmol/L]) experienced a mean 17.6% reduction in LDL-C compared with a mean 15.3% reduction in subjects in the active treatment group with baseline LDL-C in the lower half (130-159 mg/dL [3.36-4.13 mmol/L]), a difference that was not statistically significant.

## SAFETY MONITORING

There were no significant differences in adverse events or routine chemistry and hematologic laboratory tests between the treatment and placebo groups, and no serious adverse events occurred. There were no statistically significant differences between baseline and week 12 laboratory results in either group.

## COMMENT

We evaluated the lipid-lowering efficacy of a theaflavin-enriched green tea extract in subjects with mild to moderate hypercholesterolemia already consuming a low-fat diet, using a double-blind, randomized, placebo-controlled parallel-group design. The extract decreased serum total cholesterol and LDL-C by 11.3% and 16.4%, respectively. To our knowledge, this is the first human placebo-controlled trial to demonstrate an LDL-C–lowering effect from tea. Our results support the findings of several observational studies that indicate an association between tea drinking and a more favorable lipid profile[10-14] and are consistent with animal experiments demonstrating the hypolipidemic effect of tea.[15-18,20]

In observational studies as well as clinical trials with statin drugs, each 1% reduction in LDL-C results in approximately a 1.0% to 1.5% reduction in the relative risk of major cardiovascular events.[33-38] By extrapolation, if the long-term use of the tea extract produced a persistent 16% reduction of LDL-C, this could reduce the risk of major cardiovascular events by 16% to 24%.

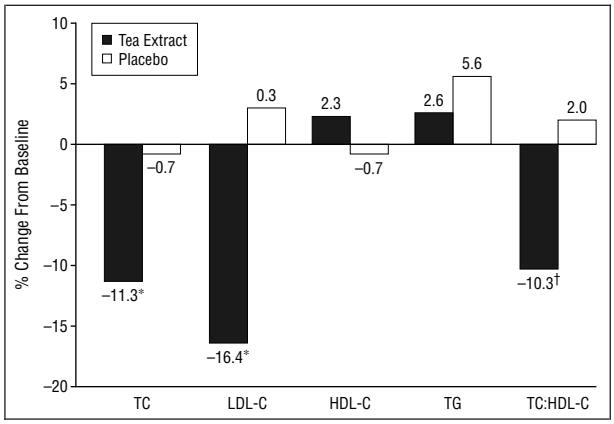


**Figure 2.** Percentage change in lipid parameters from baseline to 12 weeks by treatment group. Asterisk indicates *P*<.01 compared with baseline; dagger, *P*<.001 compared with baseline. Changes otherwise not statistically significant. TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; TC:HDL-C, total cholesterol–HDL-C ratio.

We did not examine the mechanism by which the theaflavin-enriched green tea extract lowered LDL-C in our study, but the biological plausibility of our finding has been established by the work of others, predominantly in animal models of hypercholesterolemia. Potential mechanisms include reduced micellar solubility and intestinal absorption of cholesterol,[22] increased fecal excretion of fat and cholesterol,[19-21,23] reduced hepatic cholesterol concentration,[18,39] and up-regulation of the LDL receptor in liver cells.[24]

The extract tested in this study contained 75 mg of theaflavins, 150 mg of green tea catechins, and 150 mg of other tea polyphenols in each daily capsule. Previous human tea-drinking trials tested daily exposure to theaflavins ranging in doses from 0 mg[25,27] to approximately 35 mg[25] and to catechins in doses ranging from 50 mg to 850 mg.[25,28,29] None of these studies found any significant impact on lipid and lipoprotein concentrations. We are aware of one published study in humans that tested



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the impact of a green tea extract in capsule form on lipids and lipoproteins. Princen et al[25] tested a capsule that contained 150 mg of green tea polyphenol and no theaflavins. Subjects ingested 24 capsules per day or 3.6 g of green tea polyphenol daily (equivalent to 18 cups of green tea per day and 2.5 g of catechins), and no effect on lipids was observed. While it is possible that the addition of theaflavins to catechins was responsible for the reduction in cholesterol seen in our study, it is not possible to conclude what role theaflavins, catechins, other tea polyphenols, or even the method of extract preparation may have had in the reduction of LDL-C. Additional research is necessary to determine the mechanism of action of this extract.

Several observational studies of human populations indicate that tea consumption is inversely associated with cardiovascular disease.[2-7] In support of this observation, not only does tea lower cholesterol in animal models, but it also reduces atherosclerosis. Rabbits fed an atherogenic diet plus tea have less aortic atherosclerosis than rabbits fed the same diet without tea.[16] Interestingly, green tea catechins prevent the development of atherosclerosis in apoprotein E–deficient mice fed an atherogenic diet without affecting plasma lipid levels.[40] In addition to beneficial effects of tea on lipid levels and lipoprotein levels, other proposed mechanisms for the apparent cardioprotective effect of tea include antioxidant effects,[1,2,3,41,42] improved endothelial function,[43] an estrogenic effect,[44] and anticoagulant effects.[45] Our study did not investigate any of these potential lipid-independent mechanisms associated with tea.

The subjects in our study were all urban Chinese who consumed approximately 27% of total calories from fat, 6% of calories from saturated fat, and 400 mg of cholesterol daily. By comparison, the average US resident consumes 33% of total calories from fat, 11% of total calories as saturated fat, and 256 mg of cholesterol per day.[46,47] National dietary surveys from the 1990s indicate the average urban Chinese consumed approximately 33% of calories from fat[48] and 425 mg of cholesterol per day.[49] The subjects in our study ate less dietary fat than the typical urban Chinese, perhaps because they had already been counseled to reduce their fat intake because of hypercholesterolemia. We do not know what effect the extract might have on the LDL-C level of other ethnic groups eating a diet with a different amount of fat or cholesterol.

The Third Report of the National Cholesterol Education Program Adult Treatment Panel reaffirms that in the primary prevention of coronary heart disease, diet therapy is the initial recommended intervention for lowering LDL-C.[46] Prior to advancing to drug therapy, the guidelines recommend nonpharmacologic therapeutic options—specifically viscous fiber and plant stanols and sterols—to enhance LDL-C lowering if the LDL-C goal has not been achieved with dietary therapy.[46] There is a need to identify additional nonpharmacologic therapeutic options for cholesterol lowering that have sufficient safety, efficacy, and product standardization data. There is also a need to find products that are more practical for the consumer than viscous fiber and plant stanols and sterols to permit widespread adoption. The present study represents the first step in establishing the practicality, safety, and LDL-C–lowering efficacy of a tea product. More research is needed to determine long-term safety, the effective dosing range, the optimal timing of administration, the effect of dietary fat content, drug interactions, impact when coadministered with lipid-altering medications (especially statins), and generalizability to other ethnic and patient groups.

In summary, we found that a theaflavin-enriched green tea extract administered once a day is an effective adjunct to a low-saturated-fat diet to reduce LDL-C in hypercholesterolemic adults and is well tolerated. Based on these results, we recommend larger and longer-term randomized controlled trials to confirm our findings in a more diverse population and to study the effect of this extract on other risk factors for atherosclerosis.

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*Corresponding author and reprints: David J. Maron, MD, Vanderbilt Page-Campbell Heart Institute, Vanderbilt University Medical Center, 2311 Pierce Ave, Nashville, TN 37232 (e-mail: david.maron@vanderbilt.edu).*

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