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# Green and Black Teas Inhibit Atherosclerosis by Lipid, Antioxidant, and Fibrinolytic Mechanisms

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Tea is the most widely consumed beverage in the world, second only to water. Most laypersons and scientists believe that green tea is healthier than black tea due to the low incidence of heart disease and cancer in the Orient. Here, we report the first dose−response comparison of a green and black tea on normal hamsters after long-term supplementation and on a hamster model of atherosclerosis. Both teas were equally effective in inhibiting atherosclerosis with the lower dose decreasing it 26−46% and the high dose decreasing it 48−63%. Atherosclerosis was inhibited by three mechanisms: hypolipemic, antioxidant, and antifibrinolytic. There was a significant correlation between atherosclerosis and the three mechanisms. In the normal animals, teas also caused some improvement in plasma low density lipoprotein (LDL), LDL/high density lipoprotein ratio, triglycerides, lipid peroxides, lower density lipoprotein lipid peroxides, and fibrinogen. Isolated lower density lipoprotein oxidizability was also reduced in all groups. Green and black teas were equally effective at human equivalent doses, thus confirming human intervention and epidemiology studies and providing mechanisms for teas' benefit.

**KEYWORDS: Atherosclerosis; hamster; green tea; black tea; lipids; lipid peroxidation; fibrinogen**

## INTRODUCTION

The annual worldwide per capita consumption of tea is 40 L/year (*1*). The annual per capita consumption exceeds 40 L. Total world production in 1989 was 2.45 million metric tons of which 80% was black tea (*2*). Black tea is preferred in the Western World, usually with milk, and green tea is drunken neat in the Orient. The custom of drinking iced tea began in the U.S.A. where now 75% of tea is consumed cold, but the practice is spreading to other countries. It is the manufacturing process that determines the type of tea to be produced. There are three different types of manufactured tea from *Camellia sinesis*: green (unfermented), oolong (partially fermented), and black (fully fermented). Black teas are produced by promoting the enzymatic oxidation of tea polyphenols, and these enzymes are inactivated in the manufacture of green tea (*1*). The manufacturing process is designed to either prevent or allow tea polyphenols to be oxidized by naturally occurring polyphenol oxidase enzymes in the plant. This step and further reactions convert colorless compounds to a complex mixture of orange−yellow to red−brown substances and an increase in the amount and variety of volatile compounds. Green tea is produced by rapidly steaming or pan firing the freshly harvested leaves to inactivate enzymes, preventing fermentation. Black tea is prepared by warming the leaves for 6 h and then rapidly drying them to inactivate enzymes resulting in a brisk, astringent flavor (*1*).

There is considerable evidence that tea drinking lowers the risk of heart disease and also reduces the risk of stroke. However, some studies have shown that tea did not reduce the risk. A recent meta analysis of 17 studies found that the risk of myocardial infarction was decreased 11% by increasing consumption of tea by 3 cups/day (*3*). The results of epidemiological studies relating tea and lipids are also mixed with a negative correlation in Norway among those who drank black tea (*4*) but no correlation in Japan where green tea is consumed (*5*). The effect of black tea consumption on subjects with normal lipids was determined in several short-term controlled trials. Black tea at 6 mugs/day produced no changes in lipids or blood pressure in 31 men and 34 women (*6*).

Green tea or black tea given to normal subjects at 0.9 L/day did not significantly change lipids after 4 weeks, as compared to a water control (*7*). No large-scale long-term study has yet been done on the effect of tea in subjects with elevated levels of cholesterol.

Black and green teas were found to be equally effective in increasing the total plasma radical-trapping antioxidant status after a single dose (*8*). A larger increase in human plasma antioxidant capacity has been measured after drinking a single dose of green tea as compared to black tea by measuring the ferric iron-reducing ability of plasma (*9*). A 4 week trial with 750 mL of black tea/day resulted in a small but significant increase in low density lipoprotein (LDL) lag time in 14 subjects (*10*). In another 4 week intervention trial in nonsmokers, consumption of 6 cups/day of green or black tea had no

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significant effect on plasma lipids, lipid peroxides, LDL lipid peroxides, or LDL oxidizability as measured by lag time (*7*).

Also, the results with animal models are not completely consistent, and all were done with very high doses. A diet with 1% black or green tea concentrated extract decreased plasma cholesterol in rats fed a high fat diet (*11*, *12*). Green tea given in the drinking water at 0.3% slightly, but not significantly, reduced atherosclerosis in rabbits and also increased the lag time of LDL oxidation. Black tea at the same dose was without effect (*13*). However, an older study with 0.5% black tea given to rabbits found a significant benefit for atherosclerosis (*14*). Green tea in a concentrated extract was an in vivo antioxidant and significantly inhibited atherosclerosis in the Apo E deficient mouse model (*15*). The dose in this study was equivalent to more than 50 cups of tea/day. Previously, we found that green and black tea supplementation at 1.25% in the drinking water for 2 weeks improved heart disease risk factors in both normal and cholesterol-supplemented hamsters. Green tea was significantly better than black tea in this short-term study (*16*).

Most lay people and many scientists believe green tea to have more health benefits than black tea (*17*). Green tea has more catechins than black tea due to the enzymatic oxidation of these compounds during fermentation. We and others have found that the total quantity as well as the quality of the phenolic antioxidants in green and black tea was not significantly different (*17*, *18*). There are no reports comparing the two types of tea in a long-term animal study. We therefore used our hamster model of atherosclerosis (*20*, *21*) to compare green and black tea at two doses, one comparable to those consumed by humans.

## MATERIALS AND METHODS

Male, weanling, Syrian golden hamsters were received from Charles River Breeding Laboratories (Wilmington, MA) and given commercial (nonpurified) rodent chow (Ralston Purina, St. Louis, MO) for 4 weeks. They were then separated into groups of statistically similar weight, housed three animals per cage, and allowed free access to food and liquids. Weights, fluid intake, and food consumption were measured every 2 weeks.

A comparison was made with two commercial blended teas (Lipton World Blend green and black teas). The tea (1.25%, the usual concentration for human consumption) was prepared by heating the leaves with boiling water and letting them steep for 5 min and then filtering by gravity. The teas for the hamsters were made by dilution of the 1.25% solutions. Teas were prepared fresh weekly, filtered and stored in the refrigerator, and diluted to volume before use. The polyphenol composition of these teas has been published (*22*). Teas and the control water contained Sweet 'N' Low at 10 g/L for greater palatability. There were nine animals in each group, and the experimental groups were given undiluted 1.25% tea (high dose) and 20-fold diluted 0.0625% (low dose). Half of the hamsters were given a normal chow diet and half a chow diet to which 0.2% cholesterol and 10% coconut oil was added to induce foam cell formation, the early stage of atherosclerosis, in 10 weeks. After an overnight fast, the aortas were collected for analysis and the blood was converted to plasma. Aorta % atherosclerosis, plasma lipids, plasma lipid peroxides, and the lag time of cupric-induced oxidation of LDL + VLDL from pooled plasmas were measured as previously described (*16*). Pooled LDL + VLDL lipid peroxides were measured as thiobarbituric acid reactive substances (TBARS) normalized per 10 mg of protein (*21*). Plasma fibrinogen was determined from pooled samples with a Sigma kit that measured thrombin-induced clotting time. The data were analyzed using SigmaStat (Jandel Scientific, San Rafael, CA), using a one-way analysis of variance multiple comparison test and Tukey's posthoc test for normally distributed data or a Mann−Whitney rank sum test for nonnormally distributed data.

**Table 1.** Effect of Green and Black Tea on Hamster Body Weight, Food Consumption, and Beverage Consumption (Mean ± SD) ($n = 9$ for Each Group)

| group | weight gain (g) | food consumption (g/day) | beverage consumption (mL/day) |
|---|---|---|---|
| | normal groups | | |
| control | 48 ± 7 | 18 ± 2 | 12 ± 9 |
| low dose green tea | 54 ± 15 | 15 ± 12 | 19 ± 3[a] |
| high dose green tea | 39 ± 7[a] | 17 ± 10 | 17 ± 9[a] |
| low dose black tea | 52 ± 10 | 13 ± 5 | 19 ± 9[a] |
| high dose black tea | 45 ± 11 | 17 ± 12 | 18 ± 8[a] |
| | high cholesterol groups | | |
| control | 57 ± 4 | 13 ± 3 | 11 ± 5 |
| low dose green tea | 53 ± 9 | 15 ± 5 | 14 ± 10 |
| high dose green tea | 58 ± 8 | 14 ± 8 | 16 ± 9[a] |
| low dose black tea | 65 ± 12 | 13 ± 5 | 15 ± 6 |
| high dose black tea | 58 ± 8 | 16 ± 12 | 18 ± 5[a] |

[a] Significantly different from the control group; $p < 0.05$.

**Table 2.** Plasma Lipid and Antioxidant Parameters of Control Group Hamsters (Mean ± SD)

| biochemical parameter | normal cholesterol control | high cholesterol control |
|---|---|---|
| cholesterol (mg/dL) | 109 ± 13 | 492 ± 67[a] |
| LDL (mg/dL) | 62 ± 14 | 433 ± 67[a] |
| HDL | 48 ± 4 | 51 ± 6 |
| LDL/HDL | 1.31 ± 0.29 | 8.68 ± 1.5[a] |
| triglycerides | 69 ± 16 | 333 ± 35[a] |
| % atherosclerosis | | 14.4 ± 3.2 |
| plasma TBARS ($\mu$M) | 2.23 ± 0.15 | 5.96 ± 0.39[a] |
| pooled LDL + VLDL TBARS ($\mu$M) | 5.72 | 8.81 |
| pooled LDL + VLDL lag time (h) | 1.83 | 1.22 |
| pooled plasma fibrinogen (mg/dL) | 7.28 | 15.1 |

[a] Significantly greater than normal group; $p < 0.0001$.

## RESULTS AND DISCUSSION

Data on animals' weight gain, food consumption, and beverage consumption are shown in **Table 1**. Teas had no significant effect on body weight gain except in the high dose green tea given to the normal cholesterol group where it decreased the weight gain 19%, $p = 0.02$. Food consumption was not significantly different among any of the groups, which indicates that any biochemical changes are not due to differences in the amount of food eaten by the hamsters. In the normal groups, both teas at both doses caused a significant increase in beverage consumption, possibly due to the caffeine in the teas. However, the consumption was not dose-dependent. In the high cholesterol groups, only the high dose teas group drank significantly more fluids than the control and the effect was dose-dependent.

Lipids, lipid oxidation, fibrinogen, and atherosclerosis values for the control groups are given in **Table 2**. As compared to the normal fed animals, there was a significant increase in lipids in the high cholesterol animals, a notable increase in the lipid oxidation measures as also fibrinogen. For ease in comparison of the two types of teas, results are shown in **Figure 1a**,**b** for the normal groups and **Figure 2a**,**b** for the high cholesterol groups, relative to their respective control groups. For the normal groups, there was generally a dose−response beneficial change in the lipids. There was a nonsignificant decrease in the cholesterol (10%), LDL (24%), and LDL/HDL ratio (24%) with the high dose of black tea. HDL was increased with both teas

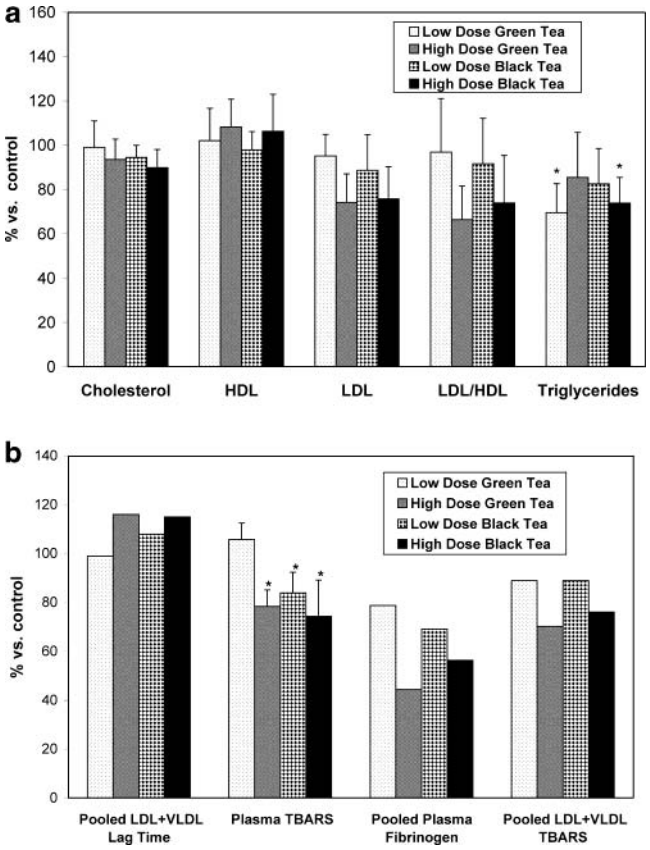


**Figure 1.** (**a**) Comparison of plasma lipids for normal animals given green and black tea at two doses; *$p < 0.05$ vs control. (**b**) Comparison of plasma lipid peroxides, LDL + VLDL oxidation markers, and fibrinogen for normal animals given green and black tea at two doses; *$p < 0.01$ vs control.

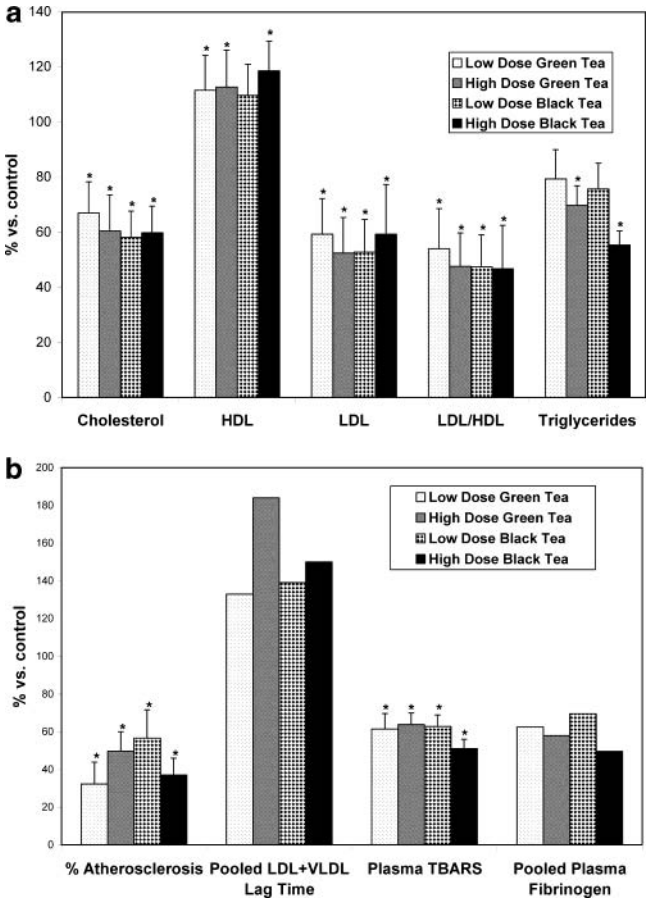


**Figure 2.** (**a**) Comparison of plasma lipids for cholesterol-fed animals given green and black tea at two doses; *$p < 0.001$ vs control, **$p < 0.02$ vs control. (**b**) Comparison of atherosclerosis, plasma lipid peroxides, LDL + VLDL oxidation markers, and fibrinogen for cholesterol-fed animals given green and black tea at two doses; *$p < 0.001$ vs control.

in a dose−response manner but not significantly. Triglycerides were significantly decreased (26%) with the high dose of black tea and almost significantly ($p = 0.06$) with the low dose of green tea (30%). There was a dose−response decrease in plasma lipid peroxides with both teas and a significant improvement with the high dose of green tea and both doses of black tea (16−26%). Also, there was a dose−response improvement in both the LDL + VLDL lag time and also a beneficial decrease in the LDL+VLDL lipid peroxides. The oxidation of these lower density lipoproteins is one of the steps leading to atherosclerosis (*23*). Plasma fibrinogen was also beneficially decreased in the normal tea groups in a dose−response manner.

As expected, the lipid parameters were greatly increased in the animals fed the high cholesterol diet as compared to those given the normal diet. The only exception was HDL, which was only slightly increased relative to the normal groups. In the high cholesterol groups, both teas at both doses significantly decreased total cholesterol (33−42%), LDL cholesterol (42−48%), and the atherogenic index LDL/HDL (46−53%) as compared to the control. HDL was increased by both teas (12−19%) but significantly only for the high dose of black tea. Both teas significantly decreased triglycerides at all doses (26−45%). Teas thus produced a greatly improved lipid profile in the high cholesterol hamsters. Green and black tea both lower cholesterol by decreasing cholesterol absorption (*24*, *25*) and green tea by increasing the LDL receptor (*26*).

Teas at both doses significantly decreased foam cell formation (43−68%), the early form of atherosclerosis. The low dose green tea group had significantly less atherosclerosis than either the low or the high black tea group ($p < 0.02$). The failure of tea to prevent atherosclerois in the rabbit model (*13*) may be attributed to the very high cholesterol levels in this animal model (over 700 mg/dL), which is considerably higher than in our model. In addition, the extent of atherosclerosis was much greater in the rabbit model. The hamster model may be a more suitable animal model for studying the antiatherosclerotic properties of antioxidants such as tea. The positive tea benefits with respect to hamster atherosclerosis in fact agree with the conclusions from human epidemiology studies (*2*, *3*).

Lag time, a measure of the antioxidants contained in the atherogenic LDL + VLDL, was lower in the high cholesterol control than in the normal cholesterol control group. This parameter increased in a dose-dependent manner for both teas (33−84%) in the high cholesterol animals. Both teas significantly decreased plasma lipid peroxides (37−41%). They were higher in the high cholesterol controls than in the normals, indicating more lipid oxidation. In both normal and high cholesterol hamsters, oxidation of LDL + VLDL as measured by lipid peroxides was decreased by green and black tea at both doses (11−30% for normal and 44−54% for the high cholesterol groups). The data were not shown in **Figure 2b** due to lack of space. Both teas in both groups in a dose-dependent fashion decreased fibrinogen (21−56% for the normal groups and 38−51% for the high cholesterol groups). Fibrinogen forms the substrate for thrombin and represents the final step in the coagulation cascade; it is essential for platelet aggregation and promotes smooth muscle cell proliferation and migration. These mechanisms make fibrinogen an independent myocardial inf-

arction, stroke, and heart disease risk factor (*27*). Fibrinogen was elevated in the high cholesterol controls as compared to the normal controls, as is the case with humans.

In general, there was no significant difference between the black tea and the green tea at the same dose for either the normal or the high cholesterol animals. The beneficial effects of teas were greater in the high cholesterol (abnormal) animals than in the normal cholesterol animals. For the high cholesterol animals, there were significant correlations between atherosclerosis and some of the mean group or pooled group parameters. Cholesterol: $r^2 = +0.829$; LDL, +0.893; LDL/HDL, +0.857; lag time, −0.699. Fibrinogen: +0.849; $p = 0.02$, 0.01, 0.01, 0.08, and 0.02, respectively, for the Pearson correlations.

Our results show that both green and black tea were equally effective in reducing early atherosclerosis in hamsters fed a cholesterol/saturated fat diet. The tea effect was multifactorial and was the result of hypolipemic, antioxidant, and hypofibrinogenic mechanisms operating. At the low dose, the high cholesterol hamster tea consumption at the end of the study corresponds to 283 mL of black tea and 285 mL of green tea for a 70 kg human, i.e., less than two 5 oz cups/day. In a later study (done after the present one using the same conditions), even 50-fold diluted green and black tea significantly inhibited hamster atherosclerosis although the effect (26 and 36%, respectively) was less than with the 20-fold diluted teas in this study (68 and 43%, respectively).

Thus, both black and green tea were beneficial at human equivalent doses in this animal model of atherosclerosis and also were beneficial for reducing risk factors for the normal animals. Although it is difficult to draw conclusions for humans from animal studies, an indication of the relevance of our work to humans is found in several recent reports. In Japan, green tea consumption was inversely associated with atherosclerosis (*28*) and cholesterol (*29*) for both men and women. A Korean study found that longer green tea consumption of subjects in a tea-growing area resulted in lower LDL and LDL/HDL (*30*). A large Chinese study found that one capsule of a concentrated black tea extract (equivalent to 7 cups of black tea/day) caused a 16% decline in LDL in hypercholesterolemic subjects on a low fat diet (*31*). In an American population with mildly elevated cholesterol, consumption of 5 cups of black tea produced significant reductions in cholesterol, LDL, and lipoprotein (a) (*32*). A U.S. epidemiology study reported that consumption of 2 or more cups of tea/day cut the risk of heart attack death in half (*33*). The positive results shown in this work and in the human studies indicate the possible long-term benefits of tea drinking, especially to subjects with elevated cholesterol, but even to normal individuals.

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