Coffee Oil Consumption Does Not Affect Serum Cholesterol in Rhesus and Cebus Monkeys[1,2]

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ABSTRACT Oil from coffee beans contains the diterpenes cafestol and kahweol, which greatly elevate cholesterol in humans. Consumption of 0.03 g coffee oil (0.86 mg cafestol and 1.04 mg kahweol)/kg body wt raised serum cholesterol by 1.27 mmol/L in volunteers. We fed coffee oil from this same batch to cebus and rhesus monkeys. Two groups of eight cebus monkeys were fed a purified diet containing 0.5% coffee oil or placebo oil (sunflower plus palm oil, 3:2, wt/wt) for 2 × seven and a half weeks in a crossover design. The daily intake of the coffee oil was 0.18 g (5.13 mg cafestol and 6.21 mg kahweol)/kg body wt, or sixfold that in the human study. Coffee oil did not affect plasma cholesterol or triglyceride concentrations compared with the placebo oil. Two groups of three rhesus monkeys were fed a commercial diet containing either 0.5% coffee oil or 0.5% placebo oil for 2 × 6 wk in a crossover design. The daily intake of coffee oil was 0.20 g (5.70 mg cafestol and 6.90 mg kahweol)/kg body wt. Again, there was no effect of coffee oil on plasma cholesterol or triglyceride concentrations. Contrary to the findings in human studies, coffee oil had no impact on plasma alanine aminotransferase activity in nonhuman primates. The cholesterol-raising effect of diterpenes from coffee oil, present in boiled coffee, seems to be specific for human primates. J. Nutr. 125: 2301–2306, 1995.

INDEXING KEY WORDS:

• *coffee* • *coffee oil* • *monkeys*
• *cholesterol* • *lipoproteins*

Boiled coffee, i.e., coffee prepared by boiling ground coffee beans with water and consumed without filtration, is widely used in Scandinavian countries. Consumption of boiled coffee has a cholesterolemic effect (Pietinen et al. 1990, Stensvold et al. 1989, Thelle et al. 1987), whereas no such effect is found with filtered coffee (Aro et al. 1987, Bak et al. 1989). Boiled coffee and its constituent lipids elevate human plasma alanine aminotransferase (EC 2.6.1.2, ALAT) activity and depress γ-glutamyltransferase (EC 2.3.2.2) activity (Weusten-van der Wouw et al. 1994). Intake of boiled coffee is associated with an increased risk of coronary heart disease (Tverdal et al. 1990).

Two constituents of ground coffee, cafestol and kahweol, are responsible for the cholesterolemic action of boiled coffee (Weusten-van der Wouw et al. 1994). These lipid-soluble diterpenes are removed by passing coffee through the paper filters commonly used in preparing coffee (Ahola et al. 1991, Van Dusseldorp et al. 1991).

It is important to have an animal model to study the mechanism of the cholesterolemic effect of coffee oil. Nonhuman primates have proved to be suitable models for studying the effects of dietary fatty acids (Chong et al. 1987), cholesterol (Ershow et al. 1981, Nicolosi et al. 1990, Stucchi et al. 1991), and protein (Terpstra et al. 1984, Von Duvillard et al. 1992) on plasma cholesterol. Here we report the lack of effect of coffee oil on plasma lipids and liver enzymes in two species of nonhuman primates.

MATERIALS AND METHODS

Cebus monkeys. These studies were conducted at the Research Foundation of the University of Massachusetts at Lowell. The monkeys were individually

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housed in a temperature-controlled room (21°C) with a 12-h light:dark cycle. Five males and eleven females were fed for 2 wk a semipurified diet containing the following (g/kg diet): casein, 84; soybean protein, 84; cystine, 2; dextrin, 265; sucrose, 264; coconut oil, 68; corn oil, 29; olive oil, 71; safflower oil, 9; cellulose (alphacel), 50; vitamin mixture[4] (Newberne-Hayes vitamin mixture, cat. no. F8280, BioServe, Frenchtown, NJ) 50; mineral mixture[5] (Ausman-Hayes vitamin mixture, cat. no. F8528, BioServe, Frenchtown, NJ), 10; choline chloride, 3; banana flavoring, 5; cholesterol, 1; and 5 g placebo oil [a mixture of sunflower oil and palm oil (3:2 wt/wt)] with the same fatty acid composition as the coffee oil.

The diet contained a calculated energy content of 18.48 MJ/kg, 54 mg cholesterol/MJ and 36% fat energy. The monkeys were then divided into two groups of eight monkeys on the basis of their total plasma and HDL cholesterol concentrations. Initial total plasma and HDL cholesterol concentrations were 4.73 ± 0.83 and 2.48 ± 0.59 mmol/L (n = 8, mean ± SD), respectively, for one group (two males and six females), and 4.80 ± 0.92 and 2.42 ± 0.65, respectively, for the second group (three males and five females). The two groups were fed the purified diet containing 0.5% coffee or placebo oil in a 2 × 7.5-wk crossover design with no washout period. The coffee oil was from the same batch as that used with human volunteers by Weusten-van der Wouw et al. (1994). The coffee or placebo oil and cholesterol were mixed with the coconut, corn and olive oil, and the complete diets were mixed with water (1 kg diet and 0.5 L water) and fed to the monkeys as a cake. Each animal received 150 g wet feed/d. The monkeys had free access to water. The calculated intake of coffee oil was 0.5 g (14.25 mg cafestol and 17.25 mg kahweol)/d or 0.18 g (5.13 mg cafestol and 6.21 mg kahweol)/kg body wt. Food-deprived cebus monkeys were anesthetized with ketamine-HCl (5 mg/kg body wt), and blood was collected from the femoral vein into tubes containing EDTA as an anticoagulant. The monkeys were maintained in accordance with the guidelines of the Committee on Animals of the University of Massachusetts at Lowell Research Foundation and the NIH *Guide for the Care and Use of Laboratory Animals* (NRC 1985).

Rhesus monkeys. The studies with rhesus monkeys were conducted at the Animal Laboratory of Utrecht University, The Netherlands. The monkeys were individually housed in a temperature-controlled room (21°C), with a 12-h light:dark cycle. Six male rhesus monkeys were used and fed a commercial pelleted primate diet[6] (Hope Farms, 3440 AB Woerden, The Netherlands). The monkeys were randomly divided into two groups of three animals. Initial total plasma and HDL cholesterol concentrations were 3.19 ± 0.29 and 2.03 ± 0.56 mmol/L (mean ± SD), respectively, for one group, and 3.59 ± 0.55 and 2.19 ± 0.12 mmol/L, respectively, for the second group. The two groups were fed the commercial diet with 50 g coconut oil and 1 g cholesterol plus 5 g coffee oil or placebo oil per kilogram diet in a 6-wk crossover study with no washout period. Again, the coffee oil was from the same batch as that used by Weusten-van der Wouw et al. (1994). The monkeys had free access to water. The diet contained a calculated energy content of 17.78 MJ/kg, 56 mg cholesterol/MJ and 21% fat energy. The coffee or placebo oil and cholesterol were mixed with coconut oil and then mixed into the powdered commercial diet. The diet was then pelleted, with each animal receiving 200 g/d. The calculated intake of coffee oil was 1.0 g (28.7 mg cafestol and 34.7 mg kahweol)/d or 0.20 g (5.70 mg cafestol and 6.90 mg kahweol)/kg body wt. Food-deprived rhesus monkeys were anesthetized with a mixture of ketamine-HCl and atropine, and blood was drawn from the external cubital vein into heparinized tubes. The experimental protocol was approved by the Animal Ethics Committee of Utrecht University.

Analytical methods. Cholesterol (Allain et al. 1974) and triglyceride (Bucculo and David 1973) concentrations were measured using enzymatic methods. Plasma HDL cholesterol was assayed after precipitation of VLDL+LDL with phosphotungstic acid/$MgCl_2$ (Assman et al. 1983). The ALAT activity in the plasma was measured using a commercial kit (Unikit II, Roche Diagnostics, 3641 RR Mijdrecht, The Netherlands). The diets were analyzed at the end of

[4]The vitamin mixture provided (mg/kg diet): ascorbic acid, 1170; inositol, 1000; taurine, 500; all-*rac*-α-tocopherol acetate, 100; nicotinamide, 80; calcium pantothenate, 50; retinyl acetate, 50; riboflavin, 16; folic acid, 12; pyridoxine hydrochloride, 8; thiamine hydrochloride, 8; cholecalciferol 6.2; menadione, 1; cyanocobalamin, 0.4; biotin, 0.4; and dextrin (carrier material), 7000.

[5]The mineral mixture provided (mg/kg diet): K_2HPO_4, 15,710; $CaCO_3$, 14,525; NaCl, 8120; $MgSO_4 \cdot 7H_2O$, 4935; $CaHPO_4$, 3630; MgO, 1600; Fe-citrate, 1350; $Mn(HSO_4)_2$, 61; $ZnCl_2$, 39; $Ca_3(PO_4)_2$, 25; $CuSO_4$, 14.5; Cr-acetate, 2; NaF, 1; and Na_2SeO_3, 0.215.

[6]The composition of the diet as provided by the manufacturer was (per kilogram diet): protein, 232 g (digestible 216 g); fat, 48 g (linoleic acid, 24 g); fiber, 27 g; other carbohydrates, 631 g; calcium, 8.2 g; phosphorus, 5.4 g; potassium, 8.3 g; magnesium, 3.4 g; sodium, 3.1 g; chlorine, 5.8 g; iron, 175 mg; manganese, 70.2 mg; zinc, 52 mg; copper, 18.1 mg; cobalt, 0.7 mg; iodine, 0.68 mg; selenium, 0.2 mg; tin, 2.8 mg; chromium, 1.5 mg; retinol, 46; cholecalciferol, 4.8; all-*rac*-α-tocopherol acetate, 97 mg; menadione, 11.8 mg; thiamine, 16.4 mg; riboflavin, 13.8 mg; niacin, 62.9 mg (available, 41 mg); pantothenic acid, 39.2 mg; folic acid, 9.3 mg; pyridoxine, 14.8 mg; choline, 2020 mg; cyanocobalamin, 40 μg; biotin, 200 μg; and ascorbic acid (measured after 2 mo storage at 20°C and 50% relative humidity), 1520 mg. The diet was based on soybean meal (46% protein, extracted and toasted); yellow dent corn; expanded whole wheat; rolled oats; low fat meat meal (85% protein, sterilized); yeast (*Saccharomyces cerevesiae*); lactalbumin; linseed; beef liver meal; alfalfa; corn/soy oil; dextrose; calcium carbonate; dicalcium phosphate; magnesium oxide; L-lysine; DL-methionine; vitamins and minerals.

the studies for moisture, protein (AOAC 1979), fat (Folch et al. 1957), fatty acid composition (Metcalfe et al. 1966) and cholesterol (Norby and Nagy 1973).

Statistics. Results (means ± SD) were statistically analyzed with a two-way repeated-measures ANOVA. Statistical analyses were done with the SigmaStat® statistical software package (Jandel Corporation, San Rafael, CA).

RESULTS

Body weights of both the cebus (n = 16) and the rhesus monkeys (n = 6) increased slightly, independent of the coffee oil supplement, during the course of the experiment. Body weights increased from 2.56 ± 0.44 to 2.90 ± 0.60 kg ($P < 0.05$) in the cebus monkeys and from 4.50 ± 0.23 to 5.06 ± 0.32 kg ($P < 0.05$) in the rhesus monkeys.

Consumption of the coffee oil compared with consumption of the placebo oil did not affect serum lipids in either the cebus or rhesus monkeys (**Fig. 1**). Plasma cholesterol concentrations in the cebus monkeys remained more or less constant during the duration of the experiments, and the same was true for the plasma triglyceride and HDL cholesterol concentrations. Plasma cholesterol concentrations at the end of the dietary periods in the group of cebus monkeys fed first the coffee oil and subsequently the placebo oil were 4.81 ± 0.78 and 4.76 ± 0.74 mmol/L, respectively; in the group fed first the placebo oil diet and then the coffee oil diet the concentrations were 5.15 ± 1.03 and 4.72 ± 0.56 mmol/L, respectively. The respective concentrations of HDL cholesterol were 2.59 ± 0.48 and 2.49 ± 0.50 mmol/L in the coffee oil-placebo oil group and 2.72 ± 0.62 and 2.53 ± 0.56 mmol/L in the placebo-coffee oil group.

The total and HDL cholesterol concentrations in the rhesus monkeys increased during the first 2 wk of the experimental diets ($P < 0.05$), but this increase was similar for both dietary groups. Plasma HDL and total cholesterol remained constant after 2 wk on the diet. Plasma triglycerides were not influenced by the dietary treatment (Fig. 1).

Coffee oil increased plasma ALAT activities in previous studies with human subjects (Weusten-van der Wouw et al. 1994), and therefore ALAT activity was also measured in the present studies with monkeys. Coffee oil did not influence plasma ALAT activities. At the end of the dietary periods, in the cebus monkeys fed first the coffee oil, and subsequently the placebo oil, ALAT activities were 29.0 ± 16.8 and 37.0 ± 26.7 U/L, and in the group first fed the placebo oil diet and then the coffee oil diet, the activities were 43.3 ± 21.8 and 32.7 ± 14.2 U/L, respectively. ALAT activities in the rhesus monkeys were 16.8 ± 8.2 and 19.4 ± 7.6 U/L and 9.6 ± 1.4 and 12.0 ± 3.1 U/L, respectively.

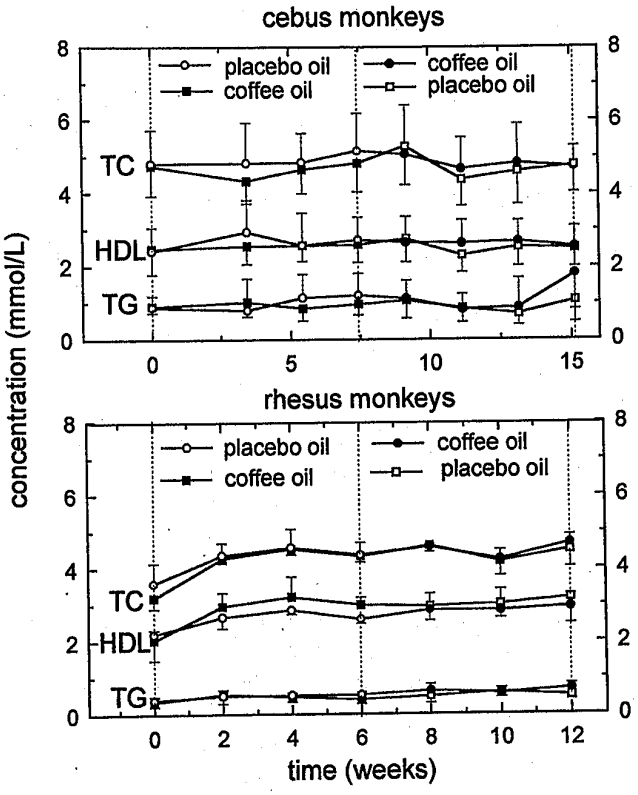

FIGURE 1 Concentrations of total cholesterol (TC), HDL cholesterol (HDL) and plasma triglycerides (TG) in cebus and rhesus monkeys fed coffee oil or placebo oil. Values are expressed as means ± SD of eight cebus monkeys or three rhesus monkeys.

DISCUSSION

The objective of the present study was to determine whether the cholesterolemic effect of coffee oil in humans could be reproduced in nonhuman primates. Humans were given 2 g coffee oil/d in previous studies (Weusten-van der Wouw et al. 1994). In a reference person of 70 kg body wt, this amount is equivalent to a coffee oil intake of 30 mg/kg body wt. The proportions of coffee oil in the diets for humans and monkeys were comparable, but monkeys have a higher food and energy intake per kilogram of body weight (**Table 1**). As a result, the monkeys were fed ~6 times more per kilogram of body weight (Table 1).

The present studies suggest that coffee oil has no effect on plasma lipid concentrations of nonhuman primates. This contrasts with our studies in large groups of human volunteers in which coffee oil caused impressive and consistent rises in serum

TABLE 1

Intake of coffee oil in the present studies in cebus and rhesus monkeys compared with that in human studies

	Cebus monkeys	Rhesus monkeys	Humans[1]
Body weight, *kg*	2.81 ± 0.55[2]	5.0 ± 0.46[2]	70
Food intake			
g/d	100[3]	200	500
g/kg body wt	35	40	7.1
Energy intake, *MJ/d*	1.85	3.56	10.0
Coffee oil intake			
g/d	0.5	1.0	2.0
g/(kg body wt·d)	0.18	0.20	0.03

[1]A typical subject participating in our published studies (Weusten-van der Wouw et al. 1994).
[2]Mean ± SD of the body wt at the end of the dietary coffee oil period.
[3]Corrected for added water; 50 g water was added to 100 g diet and each monkey received 150 g wet feed/d.

cholesterol and triglyceride concentrations (Weusten-van der Wouw et al. 1994). Other studies in our laboratory with hamsters, gerbils, rats and rabbits also failed to find an effect of coffee oil on plasma cholesterol concentrations (Weusten-van der Wouw et al. 1993). Data, however, are contradictory; Sanders and Sandaradura (1992) reported a cholesterolemic effect of boiled coffee in hamsters. Because we used coffee oil from the same batch in our studies with human subjects and with experimental animals, any possible effect of different batches of oil can be excluded.

The effects of coffee oil on the cholesterol levels of the cebus and rhesus monkeys were −0.18 ± 0.76 mmol/L in the cebus monkeys and +0.08 ± 0.35 mmol/L in the rhesus monkeys. Based on the observed standard deviations, it can be calculated that a potential coffee oil effect of at least 0.57–0.59 mmol/L would have been detected in the cebus monkeys with a statistical power of 80% with $P = 0.05$. Similarly, in the rhesus monkeys, a potential coffee oil effect of 0.50–0.56 mmol/L would have been picked up with a statistical power of 80% with $P = 0.05$. Thus, the statistical power of the present studies was sufficient to detect a coffee oil effect on serum cholesterol of at least 0.50–0.59 mmol/L, a change much smaller than that caused in humans (1.27 mmol/L) by a much lower intake of coffee oil (Weusten-van der Wouw et al. 1994).

TABLE 2

Analyzed composition of experimental diets

Component	Cebus monkeys[1]		Rhesus monkeys	
	Coffee diet	Placebo diet	Coffee diet	Placebo diet
	g/kg diet			
Dry matter	826	828	858	855
Ash	41	40	ND[2]	ND
Protein	132	128	189	192
Cholesterol, *mg*	620	770	1050	970
Total fat	132	134	110	107
Saturated	53	53	69	66
$C_{12} + C_{14} + C_{16}$	42	43	54	52
Monounsaturated	52	53	19	18
Polyunsaturated	27	28	22	23
Cafestol, *mg/100 g*	80	0	ND	ND
Kahweol, *mg/100 g*	118	0	ND	ND
P/S[3] ratio	0.5	0.5	0.3	0.3

[1]Composition of the diets to which no water was added (see Materials and Methods).
[2]ND = not determined.
[3]Polyunsaturated fatty acids/saturated fatty acids.

Commercial diets for nonhuman primates are usually composed of products of plant origin. These cholesterol-free diets are low in fat concentration (50 g/kg diet). We increased the fat and cholesterol concentrations of our experimental diets (**Table 2**) to make the composition more comparable to the diets consumed by human subjects. The effects of cafestol, kahweol and other xenobiotics on plasma cholesterol concentrations are likely to be more evident when tested in a high fat, high cholesterol diet.

The high fat content of the experimental diets may also explain the gain in body weight of both the cebus and rhesus monkeys during the experimental period. The rhesus monkeys had been transferred from a low fat (~50 g/kg diet) commercial diet to the experimental diet containing an additional 50 g coconut oil/kg diet. The cebus monkeys had been fed the high fat, high cholesterol experimental diet with the placebo oil for a period of 2 wk before starting the experiment. These 2 wk of adaptation may explain why the weight gain of the cebus monkeys was less than that of the rhesus monkeys. Further, the addition of 0.1% cholesterol to the diets may also have contributed to the increase of total plasma and HDL cholesterol concentrations in the rhesus monkeys during the first 2 wk on the experimental diets. The cebus monkeys, on the other hand, were fed a 0.1% cholesterol diet during the adaptation period of 2 wk.

Rhesus and cebus monkeys have been used to examine the effects of dietary cholesterol and the type of fat and protein on plasma lipid levels (Chong et al. 1987, Ershow et al. 1981, Nicolosi et al. 1990, Stucchi et al. 1991, Terpstra et al. 1984, Von Duvillard et al. 1992). Dietary cholesterol and the type of fat and protein have effects on plasma cholesterol concentrations and metabolism in monkeys similar to those seen in human subjects. In the present study, however, we were unable to reproduce the cholesterolemic effect of coffee oil in the monkeys. These findings suggest that the cholesterolemic effect of coffee oil is specific for humans.

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