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THE CHOLESTEROL-RAISING FACTOR FROM COFFEE BEANS

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ABSTRACT

Some coffee brewing techniques raise the serum concentration of total and low-density-lipoprotein cholesterol in humans, whereas others do not. The responsible factors are the diterpene lipids cafestol and kahweol, which make up about 1% (wt:wt) of coffee beans. Diterpenes are extracted by hot water but are retained by a paper filter. This explains why filtered coffee does not affect cholesterol, whereas Scandinavian "boiled," cafetiere, and Turkish coffees do. We describe the identification of the cholesterol-raising factors, their effects on blood levels of lipids and liver function enzymes, and their impact on public health, based on papers published up to December 1996.

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INTRODUCTION

Coffee and Coronary Heart Disease Risk

The relationship between coffee and coronary heart disease has long been controversial. In 1963, Paul et al (56) suggested for the first time that coffee drinking predisposes humans to myocardial infarction. This was not confirmed by epidemiologic studies that followed, although some did find a link (79). One complicating factor was that coffee drinkers smoke more than abstainers do (62). Indeed, smoking explained the original finding of Paul et al (57).

The uncertainties associated with epidemiologic analyses make it important to define the effects of coffee on risk factors for coronary heart disease in controlled experiments. Hypertensive effects may probably be disregarded, as the chronic impact of coffee or caffeine on blood pressure is small (79). Attention should thus be focused on the effect of coffee drinking on serum cholesterol.

Coffee and Serum Cholesterol

Much of the information on coffee and cholesterol has come from Scandinavia, which has the highest coffee consumption worldwide (20). In 1983, Thelle et al (77) found a strong association between coffee intake and serum cholesterol in Norway. They subsequently found in two experiments that withdrawal of coffee reduced cholesterol by 10% (5, 23).

However, such an association was not consistently observed in the United States or in western Europe (78). The hypothesis was raised that the brewing method was critical: Scandinavians traditionally boil coffee grounds in water and pour the fluid into a cup without filtering it, whereas Americans and western Europeans mostly use a paper filter to separate the grounds from the brew (34). Aro et al (9) showed in an experiment that "boiled" coffee indeed raised cholesterol, whereas in a parallel group filtered coffee had no effect. Bak & Grobbee (10) showed that actual boiling was not necessary: Simply incubating the coffee grounds in 93°C water in a thermos jar produced the same effect. Later experiments showed that boiled coffee lost its entire cholesterol-raising potency when it was poured through a paper filter (1, 88). The brewing method, thus, made the crucial difference.

THE DITERPENES CAFESTOL AND KAHWEOL ARE THE CHOLESTEROL-RAISING FACTORS FROM COFFEE BEANS

The question now became which factor in boiled coffee affected cholesterol. While studying the content of solid coffee particles in boiled versus filtered coffee, Zock et al (95) fortuitously found that boiled coffee, upon centrifugation, displayed a thin floating layer of oil. Analyses confirmed that boiled coffee contains some 1–2 g of lipid/liter, whereas filtered coffee contains hardly any (88). Ingestion by 10 volunteers of 1.3 g of such boiled-coffee lipids per day raised serum cholesterol by 23% (95). Later studies with oils pressed directly from coffee beans produced similar effects (47, 89, 92). Thus, the cholesterol-raising factor was a lipid.

Coffee oil largely consists of triglycerides, which do not affect serum cholesterol when consumed in small amounts (46), but it also contains some 15% of diterpene esters of fatty acids (90). Coffee oil that had been stripped of these diterpene esters no longer raised cholesterol in volunteers (92). Heckers et al (31) then showed that ingestion of 148 mg of purified diterpene alcohols per day raised cholesterol by 32%, and similar rises were observed with purified diterpene esters (81, 92).

The question now remained as to which diterpene was responsible. The major coffee diterpenes are cafestol and kahweol (Figure 1). Pure cafestol can be made by hydrogenating a mixture of cafestol and kahweol isolated from coffee oil. However, it is difficult to purify kahweol. Urgert et al (81), therefore, compared a supplement of pure cafestol with a mixture of cafestol and kahweol. Giving 63 mg of cafestol per day to 10 volunteers raised cholesterol by 17%, whereas a mixture of 60 mg of cafestol plus 51 mg of kahweol per day only

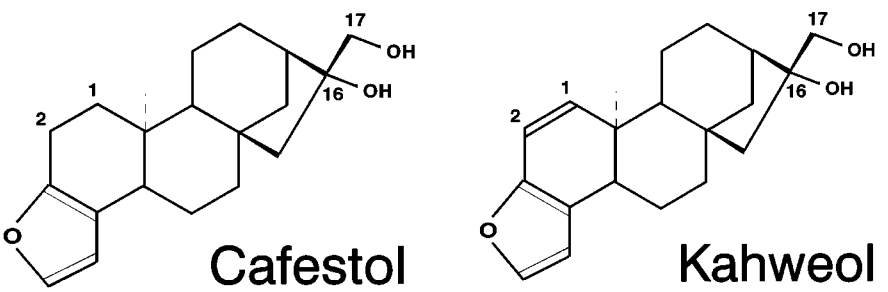

Figure 1 Structure of the coffee diterpene alcohols cafestol and kahweol. Kahweol has a double bond between the C1 and C2 carbon atoms. Diterpenes occur in coffee beans largely esterified to fatty acids at the C17 hydroxyl group.

increased cholesterol by a further 2%. This suggested that the cholesterol-raising potential of a coffee brew depends mainly on its content of cafestol, and less on that of kahweol.

COFFEE DITERPENES RAISE LOW-DENSITY-LIPOPROTEIN CHOLESTEROL AND TRIGLYCERIDES, AND ALSO AFFECT LIPOPROTEIN(a)

Experimental Evidence

Eleven trials with humans given supplements of known diterpene content had been published by December 1996 (Table 1). All subjects were healthy and normolipidemic. For this review, we performed a meta-analysis on these 11 trials, using as the independent variables the intakes of cafestol and kahweol per day and as the dependent variables the mean changes in serum variables after four weeks of treatment.

CHOLESTEROL In the combined trials, serum total cholesterol rose by 0.13 mmol/liter (5.0 mg/dl) with each 10 mg of cafestol and by 0.02 mmol/liter (0.9 mg/dl) with each 10 mg of kahweol consumed per day for four weeks. This confirms that cafestol raises cholesterol more than kahweol does. The effect was linear up to 100 mg of cafestol per day (Figure 2), the amount present in 15–30 cups of boiled coffee (28, 85). About 80% of the rise in total cholesterol was accounted for by LDL cholesterol, and the rest was due to a rise in very low-density lipoproteins. High-density lipoproteins may fall slightly when cafestol and kahweol are ingested (81, 92, 95). The pattern of changes induced by various diterpene-rich preparations in these 11 trials was in good agreement with that seen with boiled coffee (1, 8–10, 88).

TRIGLYCERIDES Volunteers given boiled coffee (1, 8–10, 88), or preparations rich in coffee diterpenes (31, 47, 81, 84, 89, 92), showed a marked rise in serum triglycerides. Again, cafestol was the major responsible factor; in 10 volunteers, cafestol alone raised triglycerides by 86%, whereas addition of a similar amount of kahweol to the treatment further increased the response by only 7% (81). Our regression analyses of 11 trials produced the same result; triglycerides rose by 0.08 mmol/liter (7.3 mg/dl) with each 10 mg of cafestol and by 0.01 mmol/liter (1.2 mg/dl) with each 10 mg of kahweol consumed per day for two to six weeks (Figure 2). However, most of the rise in triglycerides may subside with chronic intake of coffee diterpenes (see below).

LIPOPROTEIN(A) Lipoprotein(a), which consists of an LDL particle attached to apolipoprotein(a), is a risk factor for cardiovascular diseases (17). *Trans* fatty

Table 1 Summary of experiments in which supplements of known coffee diterpene content were given to volunteers[a]

Investigators	Design	Test period (weeks)	No. of subjects	Treatment	Dosage		Serum responses		
					Cafestol (mg/day)	Kahweol (mg/day)	Cholesterol (mmol/liter)	Triglycerides (mmol/liter)	ALT[b] (U/liter)
Zock et al (95)	Before/after	6	10	Fat from boiled coffee	64[c]	56[c]	1.06**	0.51**	10**
Weusten-van	Parallel	4	16	Placebo oil	0	0	−0.04	0.00	1
der Wouw et al (92)			16	Coffee oil	85	103	1.23**	0.83**	41**
			15	Coffee oil rich in nontriglycerides	81	98	1.19**	0.75**	47**
			16	Coffee oil poor in nontriglycerides	22	26	0.83**	0.34**	18**
	Parallel	4	16	Placebo oil	0	0	−0.06	−0.02	4
			12	Coffee oil	57	69	1.21**	0.81**	38**
			15	Coffee oil without diterpenes	0	0	0.04	−0.02	0
	Before/after	6	3	Pure cafestol + kahweol	73	58	1.71*	1.83	31
Heckers et al (31)	Parallel	4	5	Placebo	0	0	−0.23	−0.05	—
			5	Pure cafestol + kahweol	89	59	1.24[d]	0.55[d]	—
Urgert et al (84)	Before/after	3	15	Coffee grounds	43	55	0.67**	0.34**	13**
	Parallel	3	7	Placebo	0	0	0.01	0.06	3
			7	Coffee grounds	39	49	0.66**	0.36*	21*
Mensink et al (47)	Cross-over	3	5	Robusta oil	40	2	0.53	0.49**	13
			6	Arabica oil	72	53	0.65*	0.54**	17*
Van Rooij et al (89)	Parallel	6	12	Placebo oil	0	0	0.07	0.06	−4
			12	Robusta oil	29	1	0.52	0.14	9
			12	Arabica oil	68	85	1.14**	0.81**	64**
Urgert et al (81)	Cross-over	4	10	Pure cafestol	64	1	0.79**	0.65**	18**
				Pure cafestol + kahweol	60	51	0.94**	0.71**	46**
Urgert et al (83)	Parallel	24	24	Filtered coffee	1	1	−0.05	0.13	−1
			23	Cafetiere coffee	38	33	0.29*	0.19	8**

[a]Response different from the control group in parallel studies, or different from zero in cross-over studies and studies with a before/after design: *, $P < 0.05$; **, $P < 0.01$.

[b]In case of different assays for alanine aminotransferase (ALT), activities were recalculated by multiplying the response by the ratio of the reported upper limit of normal to our upper limit of normal.

[c]Estimated from a total amount of diterpenes of 120 mg.

[d]No statistical testing provided.

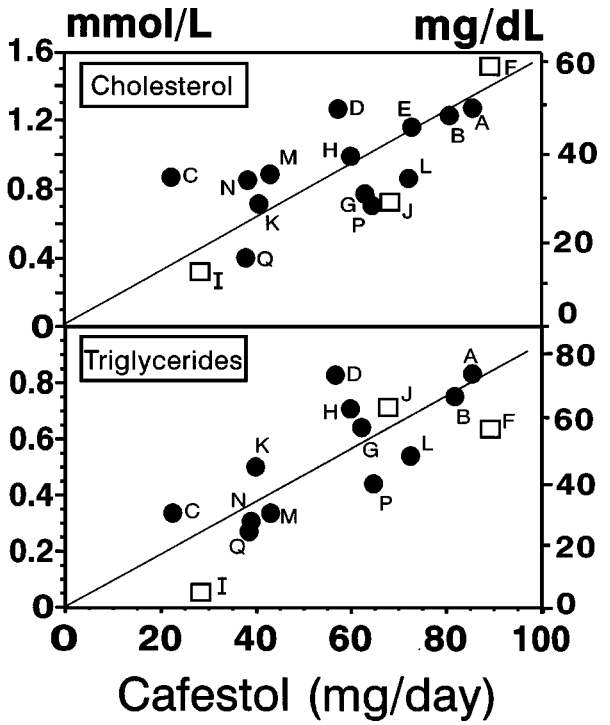

Figure 2 Relation of daily cafestol intake with mean changes in cholesterol (*upper panel*) and triglyceride levels (*lower panel*) across 11 short-term experiments carried out by the Wageningen group (*circles*) and others (*squares*). Responses were adjusted for the mean changes in the concurrent control group, if present. Those for cholesterol were recalculated to the change after four weeks of treatment. Codes refer to treatment groups in different studies: A, coffee oil (92); B, coffee oil enriched in nontriglyceride coffee lipids (92); C, coffee oil depleted in nontriglyceride coffee lipids (92); D, coffee oil (92); E, mixture of pure diterpene esters (92); F, mixture of pure diterpene alcohols (31); G, pure cafestol esters (81); H, pure cafestol plus kahweol esters (81); I, robusta oil (89); J, arabica oil (89); K, robusta oil (47); L, arabica oil (47); M and N, coffee grounds (84); P, lipid-rich extract from boiled coffee (95); Q, cafetiere coffee (values measured after four weeks of treatment) (83). Least-square best-fit equations were: Δ cholesterol (mmol/liter) $=$ $0.015 \times$ cafestol (mg/day), and Δ triglycerides (mmol/liter) $= 0.009 \times$ cafestol (mg/day).

acids are the only dietary compounds that consistently affect lipoprotein(a) (4, 49, 52). Coffee diterpenes also proved effective; in four of the trials done by the Wageningen group, each 10 mg of cafestol (plus kahweol) per day reduced serum lipoprotein(a) by 0.5 mg/dl, or 4% after four weeks (R Urgert, MPME Weusten-van der Wouw, R Hovenier, S Meyboom, AC Beynen & MB Katan, unpublished observation). However, there was a marked disparity between short- and long-term intake of diterpenes (see below).

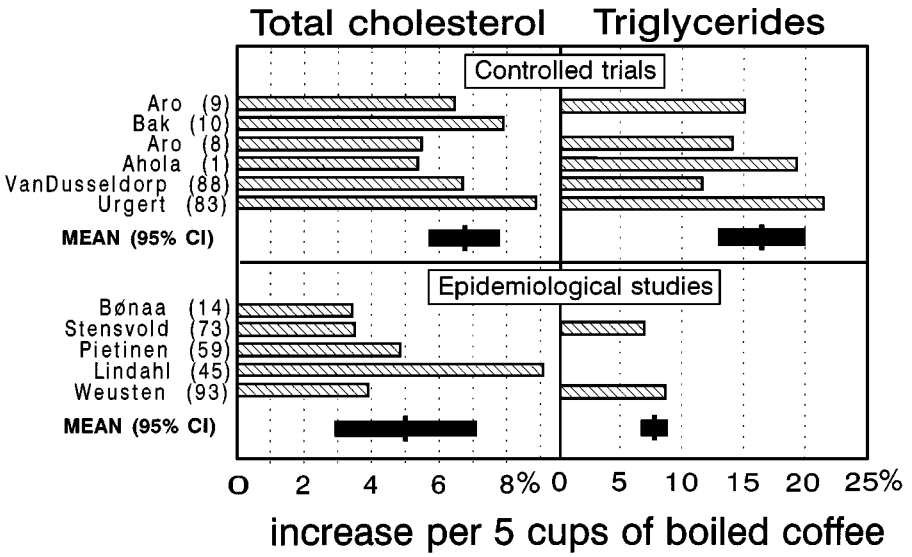

Figure 3 Percentage increases in serum cholesterol and triglyceride levels with each five cups of boiled or cafetiere coffee consumed per day in controlled trials (*upper panels*), and percentage differences with each five cups consumed per day between consumers of boiled versus filtered coffee in epidemiologic studies (*lower panels*). Black bars indicate the 95% confidence interval (CI) of the mean response per five cups.

Epidemiological Evidence

Observational studies in Norway (14, 73, 92), Finland (59), and Sweden (45) that compared chronic users of boiled to those who used filtered coffee provide insight into effects of chronic exposure to coffee diterpenes.

CHOLESTEROL In the five observational studies, chronic intake of five cups of boiled coffee per day raised serum cholesterol on average by 5%. Controlled trials with unfiltered coffee yielded an estimate of 6.8% per five cups (Figure 3). Therefore, the effect as measured in epidemiologic studies may have been slightly attenuated by measurement errors. However, a partial return of serum cholesterol to baseline values was observed in a long-term experiment with 0.9 liter of cafetiere coffee per day (83): Serum cholesterol was raised by 10% after three months of intake, but the effect was reduced to 6% after six months of intake (Figure 4). Therefore, chronic intake of cafestol permanently raises cholesterol, but trials lasting fewer than three months may slightly overestimate the effect.

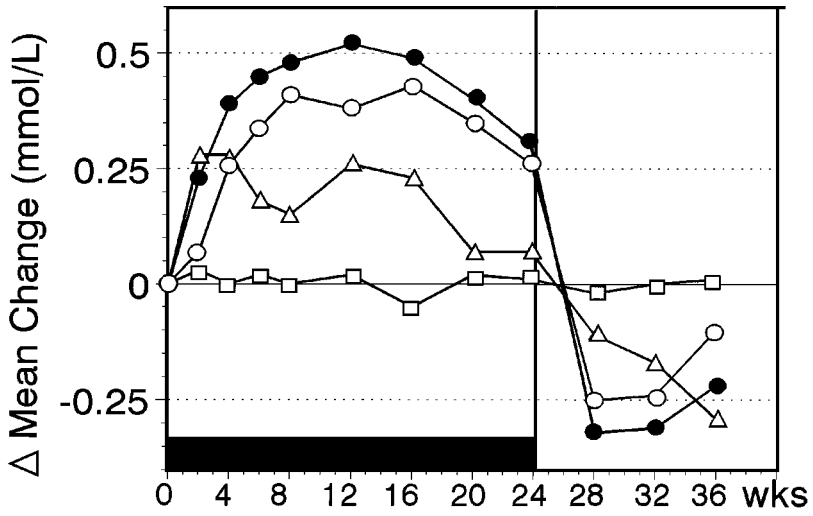

Figure 4 Mean changes in serum levels of total cholesterol (*closed circles*), triglycerides (*triangles*), low-density-lipoprotein cholesterol (*open circles*), and high-density-lipoprotein cholesterol (*squares*) in 22 subjects consuming 0.9 liter of cafetiere coffee per day for 24 weeks (83). For each time point, the mean changes from baseline occurring in 24 subjects consuming filtered coffee were subtracted from the changes in the cafetiere coffee consumers, to correct for random drifts in time. The treatment period is indicated by a horizontal black bar. No treatment was given in the follow-up period.

TRIGLYCERIDES Stensvold et al (73) found a negative association between intake of boiled coffee and serum triglycerides in Norwegians. An even stronger negative trend was observed for filtered coffee, leaving a positive net effect of 7% per five cups of boiled coffee. A similar difference between boiled- and filtered-coffee drinkers was found by Weusten-van der Wouw et al (92). In controlled trials, rises in triglycerides of up to 22% per five cups of boiled or cafetiere coffee were found (Figure 3), which suggests that most of the effect is transient with chronic intake. Indeed, 0.9 liter of cafetiere coffee per day raised triglycerides by 26% in the first month, but the effect had fallen to only 7% after six months of intake (Figure 4).

LIPOPROTEIN(A) Only one epidemiologic study has examined the effect of coffee type on serum lipoprotein(a); in 150 Norwegian, boiled-coffee drinkers, the median level of lipoprotein(a) was 65% higher than in 159 matched filtered-coffee drinkers (86). This contradicts the lipoprotein(a)-reducing capacity of diterpenes observed in clinical trials. Although a chance finding cannot be excluded, it may imply that coffee diterpenes only reduce lipoprotein(a) levels in the short run.

In summary, most of the rises in total and LDL cholesterol caused by coffee diterpenes persist with chronic intake, whereas most of the rise in triglycerides subsides. Coffee diterpenes reduce serum lipoprotein(a) in the first months of intake only. These observations have implications for experiments on the relationship between diet and lipoproteins in general; caution is needed in extrapolating results from studies lasting weeks—or even months—to chronic intakes, and corroborative evidence should always be sought in long-term trials or epidemiologic observations.

HUMANS ARE MORE SENSITIVE TO COFFEE DITERPENES THAN ANIMALS ARE

The mechanism by which coffee diterpenes affect lipid metabolism is largely unknown. Halvorsen et al studied the involvement of the LDL receptor, which is located on cell membranes and is responsible for the removal of LDL cholesterol from the bloodstream. Cafestol decreased the uptake of LDL cholesterol into human fibroblasts (30) and hepatoma cells (29) but raised it in an intestinal cell line (63). More studies are needed to clarify this discrepancy.

The effects of cafestol and kahweol seem to be unique to *Homo sapiens* (Figure 5). The same batch of coffee oil that raised cholesterol in humans (92) produced no effect in Cebus or Rhesus monkeys in two different laboratories (76) (Figure 5). Sanders & Sandaradura (69) reported that Syrian hamsters responded to boiled coffee, but an attempt to replicate this was unsuccessful (11), as were other studies with hamsters (48, 65). Diterpenes raised cholesterol in only one (3) out of three (3, 11, 33) studies with Wistar rats, and no effect was found in gerbils (48) or rabbits (93). The absence of effect could not be explained by differences in dosage, mode of administration, treatment duration, or cholesterol content of the background diet. One may speculate that differences in absorption or metabolism of coffee diterpenes account for this marked species specificity. The negative results in a range of animal species emphasize the need to rely on human data.

THE LIVER IS THE TARGET ORGAN FOR COFFEE DITERPENES

Intake of coffee diterpenes (84, 89, 92) or unfiltered coffee (83, 92) raised the serum activity of alanine aminotransferase in volunteers. In a pooled analysis of 147 volunteers who received diterpenes in our own trials, each 10 mg of cafestol or kahweol per day raised alanine aminotransferase by 2–3 U/liter, or 8–12% (R Urgert & MB Katan, unpublished observation). Aspartate aminotransferase usually also rose, but less (81, 83, 84, 89, 92).

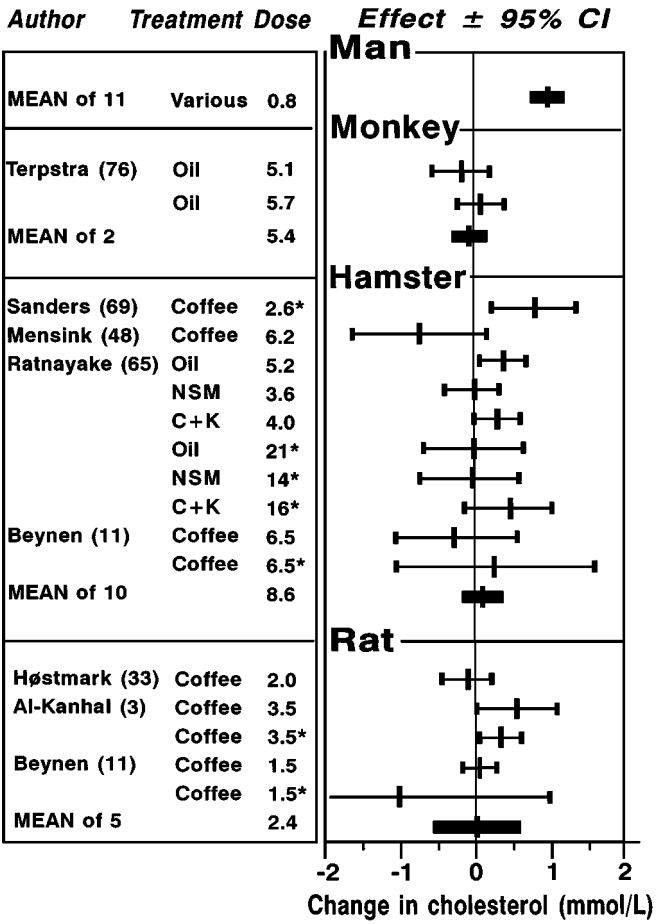

Figure 5 Comparison of the effect of cafestol in man with that in various animal species. Bars represent the 95% confidence intervals of the treatment effects. Treatment periods varied from 4 to 20 weeks. Oil, coffee oil; coffee, boiled coffee; NSM, nontriglyceride lipid fraction from coffee beans; C + K, purified cafestol and kahweol. Dose is expressed as milligrams per day of cafestol per kilogram of body weight, and high-fat or high-cholesterol background diets are indicated by an asterisk (*). The value for man represents the overall mean change in cholesterol in 11 experiments in which preparations of known diterpene content were given (cf Figure 2).

A rise of liver enzyme activity in serum may indicate injury to hepatocytes (40). This is not due to cholestasis, as coffee diterpenes reduce rather than raise the serum activity of γ-glutamyltransferase and alkaline phosphatase (81, 83, 84, 92). It is unlikely that a perturbation of liver cell function explains the effects of coffee diterpenes on blood lipids, because both cafestol and kahweol raise aminotransferases, but kahweol has little effect on blood lipids (81).

DITERPENE LEVELS IN COMMERCIAL ROAST AND GROUND COFFEES

The main commercial species of coffee are arabica and robusta coffee. Robustas contain no kahweol and less cafestol than arabicas (90); intake levels of diterpenes may thus be reduced by increasing the proportion of robustas in coffee blends. However, in the United States and western Europe, consumers prefer the taste of arabicas (20). As a result, diterpene levels in commercial roast and ground coffees in these countries are fairly constant, 400–500 mg each of cafestol and kahweol per 100 g of grounds (85). Diterpene levels in coffee beans are not affected by decaffeination and are affected little by roasting (51, 85).

In addition to cafestol, robustas also contain some 16-*O*-methylcafestol (72); the effects of this diterpene in man are unknown. Its levels are negligible in blends with a high proportion of arabicas (85), and five cups of unfiltered coffee brewed with pure robusta grounds will provide only 2–3 mg of 16-*O*-methylcafestol. This is probably too low to substantially affect blood lipids.

DITERPENE LEVELS IN COFFEE DEPEND ON BREWING TECHNIQUE

Extraction of Diterpenes into Coffee Brew

About 10% of the diterpenes present in the grounds used to make unfiltered coffee ends up in the brew, either in oil droplets or in small bean particles (84). In volunteers who consumed oily solutions of diterpenes, recovery of coffee diterpenes from feces was about 5%, compared with 25% in subjects who consumed coffee grounds (82). This suggested that most of the diterpenes ingested from the grounds are absorbed. Indeed, intake of 8 g dry weight of coffee grounds containing 39–55 mg of each diterpene per day for three weeks raised serum cholesterol by 0.65 mmol/liter in volunteers (84). Diterpene analyses of coffee brews should thus include the contribution of grounds floating in the brew. In addition, frequent ingestion of coffee beans or of grounds with turbid coffee brews should be avoided.

Brews with Low Levels of Diterpenes

FILTERED COFFEE Diterpenes do not pass through a paper filter (Table 2), which explains why controlled trials have shown no impact of filtered coffee on blood lipids (1, 10, 75, 88). Fried et al (22) found that 720 ml of filtered coffee per day raised serum cholesterol by 0.25 mmol/liter after four weeks relative to no coffee. However, no rise was seen in the groups drinking 360 ml of regular coffee per day or 720 ml of decaffeinated coffee per day; therefore, the effect seen might be due to chance.

INSTANT COFFEE Instant (or soluble) coffee is consumed worldwide (20). It is almost devoid of cafestol and kahweol (Table 2). Burr et al (13) found that five cups of instant coffee per day raised serum cholesterol by 0.12 mmol/liter in volunteers. No rise was observed in other trials of instant coffee (7, 12, 32, 66), and its effect on blood lipids—if any—should be small.

PERCOLATED COFFEE Percolated coffee (Figure 6) was popular in the United States until a decade ago. Although boiled and unfiltered, it is poor in diterpenes (Table 2). In the percolator pot, the brew is constantly recirculated through a bed of grounds, which likely functions as a filter cake, retaining the lipids. Whatever the mechanism, predicted effects of percolated coffee on blood lipids are minimal, although this has not yet been verified in human experiments.

Brews with Moderate Levels of Diterpenes

MOCHA COFFEE Mocha coffee (Figure 6) is common in Italy and Spain (20). Based on diterpene contents, each five cups of mocha per day should raise serum cholesterol by 0.13 mmol/liter (5.4 mg/dl) (Table 2, Figure 2). Observational studies in Italy (19, 55, 68) and Spain (67) are compatible with a cholesterol-raising effect of mocha, but experiments (18, 21, 70) have failed to confirm this. These studies may have suffered from insufficient power, due to short treatment periods (21) and low dosages (18, 70). However, a major lipid-raising effect of mocha coffee consumption appears excluded.

ESPRESSO COFFEE The concentration of diterpenes per 100 ml of espresso is high (64, 85). However, in Italy, espresso coffee is served in quantities as small as 25 ml (58), and absolute levels per cup are moderate (Table 2). D'Amicis et al (18) found that three cups of espresso per day non-significantly raised total cholesterol, 0.10 mmol/liter, and LDL cholesterol, 0.15 mmol/liter, relative to tea. This is consistent with a moderate effect of espresso on serum cholesterol.

Espresso coffees sampled in Italy provided more cafestol per cup than those from other countries (85). This is partly explained by the ratio of grounds to water, which is highest in Italian espresso and is a major determinant of diterpene levels in unfiltered coffee (85). In view of the increasing popularity

Table 2 Reported levels of coffee diterpenes in various coffee brews, and the estimated effect on serum cholesterol of consumption of five cups of coffee per day[a]

	Ratnayake et al (64)	Urgert et al (85)		Gross et al (28)		MEAN		Effect on serum cholesterol with five cups/day[b] (mmol/liter)
Coffee type	Cafestol or kahweol[c] (mg/cup)	Cafestol (mg/cup)	Kahweol (mg/cup)	Cafestol (mg/cup)	Kahweol (mg/cup)	Cafestol (mg/cup)	Kahweol (mg/cup)	
Paper filtered	0.1	0.1	0.1	<0.1	<0.1	0.1	0.1	<0.01
Instant	0.1	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Percolator	—	0.3	0.3	—	—	0.3	0.3	0.02
Mocha	—	1.1	1.4	2.3	2.3	1.7	1.9	0.13
Espresso	3.6	1.5	1.8	1.0	1.0	2.0	2.1	0.15
Cafetiere	1.6	3.5	4.4	—	—	2.6	3.0	0.20
Turkish	3.4	3.9	3.9	5.3	5.4	4.2	4.2	0.32
Boiled	8.4	3.0	3.9	7.2	7.2	6.2	6.5	0.47

[a]Cup sizes are 150 ml for filtered, instant, cafetiere, and boiled coffees; 60 ml for Turkish and mocha coffees; and 25–50 ml for espresso coffees.

[b]Estimations are based on the assumption that each 10 mg of cafestol consumed per day raises cholesterol by 0.13 mmol/liter, and each 10 mg of kahweol per day raises it by 0.02 mmol/liter (cf Figure 2).

[c]Ratnayake et al (64) reported total diterpene content; values are calculated assuming that levels of kahweol and cafestol were equal.

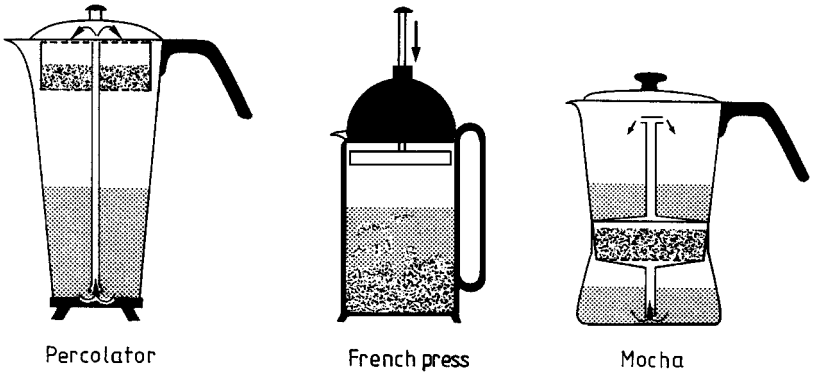

Figure 6 Brewing principles of percolated, cafetiere (French press), and mocha coffee.

of espresso worldwide (34), future studies should address other factors that may affect diterpene levels, such as brewing device, contact time of steam with grounds, and mesh width of the filter grid.

Brews with High Levels of Diterpenes

CAFETIERE COFFEE Cafetiere coffee (Figure 6)—known as French press coffee in the United States—is fairly uncommon, though its popularity is increasing (34). Based on its diterpene content, five cups per day are estimated to raise serum cholesterol by 0.13–0.27 mmol/liter (Table 2, Figure 2). The cholesterol-raising potential of cafetiere coffee was confirmed in a controlled trial (83); 0.9 liter of strong cafetiere coffee per day raised cholesterol by up to 0.52 mmol/liter (Figure 4).

TURKISH COFFEE Turkish coffee is consumed in Greece, the former Yugoslavia, Turkey, and the Middle East including Israel ("mud" coffee), and by Muslims in various countries. Five cups provide 21 mg of each diterpene, which with daily consumption will raise serum cholesterol by 0.32 mmol/liter (13 mg/dl) (Table 2, Figure 2). However, diterpene levels fluctuate strongly with the amount of grounds floating in the brew, and levels of up to 50 mg of each diterpene per five cups have been reported (85). Studies in Israel (25, 37, 38) and in Serbia (35) have indeed shown an association of cholesterol with coffee intake, but the effects of Turkish coffee have not yet been examined experimentally. Its diterpene content suggests that it may be as least as effective in raising cholesterol as is boiled coffee.

BOILED COFFEE Differences in the ratio of coffee grounds used per liter of water may explain the large differences in reported diterpene levels of Scandinavian boiled coffee (Table 2). On average, five cups per day are estimated to raise

cholesterol levels by 0.47 mmol/liter (Table 2, Figure 2); this is in agreement with results of experimental (1, 2, 8–10, 88) and epidemiologic studies (14, 45, 59, 73, 92).

Decaffeinated Coffee Brews

Superko et al (75) found in a large trial that decaffeinated filtered coffee raised LDL cholesterol by 0.23 mmol/liter compared with regular coffee. Diterpene levels of beans are unaffected by decaffeination (51, 85). Therefore, to explain the effect of decaffeinated filtered coffee as seen by Superko et al (75), one has to assume that besides diterpenes, there is a second cholesterol-raising factor in coffee beans, which is somehow introduced or activated by decaffeination, and which passes through a paper filter. We find this unlikely, especially in view of the negative results of other trials of decaffeinated filtered coffee (22, 87, 91). For lack of a better explanation we ascribe the finding of Superko et al (75) to chance, though the large number of subjects argues against that.

PUBLIC HEALTH CONSIDERATIONS

Risk of Coronary Heart Disease

Filtered, instant, and percolated coffee contain negligible levels of diterpenes (Table 2). The switch from percolated to filtered coffee in the United States thus appears not to have contributed to the fall in cholesterol levels over the last decades (24). The low intake of brews other than filtered and instant coffee in western Europe also excludes a major association with blood lipids in these countries. Little is known about effects of coffee or caffeine intake on other risk factors for cardiovascular diseases, such as oxidizability of LDL particles, vascular proliferation, or thrombosis. However, prospective cohort studies from the United States and western Europe mostly failed to find a link between coffee intake and cardiovascular disease (26, 39, 50), and a major effect of filtered, percolated, and instant coffee seems unlikely.

In the United States, about 15% of coffee consumed is decaffeinated (20), and those who use decaffeinated coffee often do so because of health concerns (44, 71). In a study of 46,000 health professionals in the United States, Grobbee et al (27) actually found a 63% higher risk of coronary mortality in consumers of decaffeinated coffee compared with coffee abstainers. As this association was not seen in a cohort of 86,000 women in the United States studied by Willett et al (94), there is no consistent evidence that filtered decaffeinated coffee raises coronary risk. However, there is no evidence for a protective effect either; the major proven benefit of decaffeinated coffee is that it does not interfere with falling asleep.

Boiled coffee used to be the dominant type in Scandinavia, but nowadays more than three quarters of Scandinavians use filtered coffee. This switch in

brewing practices is thought to explain one third (6) to one half (79) of the 10% fall in serum cholesterol in Scandinavia since 1970, and to have contributed significantly to the concurrent fall in coronary mortality (36, 60). This was supported by results of the National Health Screening Service in Norway, which examined a population largely consisting of boiled-coffee drinkers. Over the period from 1980 to 1986, a relative risk for coronary mortality of 3.3 was found in heavy coffee drinkers versus abstainers (80). The risk was reduced to 1.4 after six more years of follow-up (74), which may be due to a change in brewing practices. Thus, both experimental and epidemiologic studies suggest that a high intake of boiled coffee raises the risk of dying from coronary heart disease.

No prospective studies have examined the effects of other unfiltered brews. Because of their moderate amounts of cafestol and kahweol, mocha and espresso coffee appear harmless with consumption of a few cups per day. Turkish and cafetiere coffee are rich in diterpenes, and a recommendation to limit their use in favor of filtered or instant coffee seems justified in patients with a high cholesterol level or an increased coronary risk.

Risk of Liver Disease

Could the perturbation of liver cells by diterpene ingestion as suggested by rises in serum alanine aminotransferase activity affect hepatic health in consumers of unfiltered coffee? Alanine aminotransferase activity remained raised during half a year of daily intake of cafetiere coffee (83), but it was not raised in life-long consumers of boiled (92) or espresso coffee (15). Mortality rates of liver cirrhosis have been typically low in Scandinavian countries and appear to have been unaffected by the nationwide switch to filtered coffee (43). Also, habitual coffee drinkers have lower serum γ-glutamyltransferase levels than nondrinkers have (15, 42, 53, 54, 61)—a finding that might have a bearing on the association of coffee use with a reduction in the risk of alcoholic liver cirrhosis (16, 41). The negative relation with γ-glutamyltransferase was stronger for boiled than for filtered coffee (53). Therefore, clinically relevant damage to liver cells in healthy subjects drinking unfiltered coffee appears unlikely. However, subclinical hepatic injury cannot be excluded at the present time, and patients with elevated alanine aminotransferase levels would do well not to drink more than a few cups of boiled, Turkish, or cafetiere coffee per day.

CONCLUSIONS

Coffee beans and some coffee brewing techniques—though not filtered or instant coffee—contain the diterpenes cafestol and kahweol. They are not removed by decaffeination. Cafestol, and to a lesser extent kahweol, raises serum total and LDL cholesterol in humans. Patients at increased risk of heart disease who drink much coffee should thus be advised to select brews low in

diterpenes. Triglycerides also rise with cafestol intake, but the effect could be transient with chronic intake. Both cafestol and kahweol appear to affect the integrity of liver cells, as suggested by a modest rise of alanine aminotransferase activity in serum. All effects are reversible after withdrawal of the diterpenes.

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