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PHARMACOKINETICS AND DISPOSITION

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Influence of menthol on caffeine disposition and pharmacodynamics in healthy female volunteers

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Abstract *Objectives*: The present study was undertaken to determine whether a single oral dose of menthol affects the metabolism of caffeine, a cytochrome P_{450} 1A2 (CYP1A2) substrate, and pharmacological responses to caffeine in people.
Methods: Eleven healthy female subjects participated in a randomized, double-blind, two-way crossover study, comparing the kinetics and effects of a single oral dose of caffeine (200 mg) in coffee taken together with a single oral dose of menthol (100 mg) or placebo capsules. Serum caffeine concentrations and cardiovascular and subjective parameters were measured throughout the study.
Results: Co-administration of menthol resulted in an increase of caffeine t_{max} values from 43.6 ± 20.6 min (mean ± SD) to 76.4 ± 28.0 min ($P < 0.05$). The C_{max} values of caffeine were lower in the menthol phase than in the placebo phase, but this effect was not statistically significant ($P = 0.06$). $(AUC)_{0-24}$, $(AUC)_{0-\infty}$, terminal half-life and oral clearance were not affected by menthol. Only nine subjects' cardiovascular data were included in the analysis because of technical problems during the measurements. After caffeine, heart rate decreased in both treatment phases. The maximum decrease in heart rate was less in the menthol phase (-8.9 ± 3.9 beats/min) than in the placebo phase (-13.1 ± 2.1 beats/min) ($P = 0.024$). There were no statistically significant differences in systolic and diastolic blood pressures between the two treatments.
Conclusions: We conclude that a single oral dose of pure menthol (100 mg) delays caffeine absorption and blunts the heart-rate slowing effect of caffeine, but does not affect caffeine metabolism. The possibility that menthol slows the absorption of other drugs should be considered.

Keywords Menthol · Caffeine · Monoterpenes

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Introduction

Menthol ($C_{10}H_{20}O$) is a cyclic terpene alcohol, naturally occurring in the volatile oils of various species of mentha [1]. It has a pleasant odor and taste, and has been used for many years in a wide variety of products ranging from pharmaceutical preparations to flavor food, toothpastes, confectionery, cigarettes and pesticides.

Peppermint oil (the major individual constituent of which is menthol) has long been used as a carminative for gastrointestinal symptoms [2]. Infusions or decoctions of leaves from *Mentha piperita* are commonly used in herbal remedies for the treatment of digestive disorders in our country [3].

Despite widespread human exposure to menthol and other monoterpenes found in essential oils, the effects of these substances on xenobiotic metabolism are not well characterized. Some of the terpenoids used in pharmaceutical preparations and as constituents of food induce or inhibit drug metabolizing activities of liver in vitro. Madyastha et al. demonstrated the ability of L-menthol to induce the hepatic microsomal cytochrome P_{450} and reduced nicotinamide adenine dinucleotide phosphate

(NADPH)-cytochrome c reductase with oral administration to rats [4]. A further study on the effects of several terpenoid compounds on cytochorome P_{450} levels in rat liver was carried out by Austin et al. In this study, the induction of hepatic CYP2B subfamily after in vivo treatment of rats with menthol was reported [5]. The inhibiting effects of menthol on rat liver CYP2B1 and CYP1A2 isoenzymes were described by De-Oliveira et al. [6]. CYP1A2 inhibition was very weak in this in vitro study. In recent studies, peppermint oil was reported to inhibit CYP3A4 activity in rat and human liver microsomes and to enhance the oral bioavailability of the CYP3A4 substrate felodopine in people [7, 8].

Caffeine is one of the most widely and frequently consumed xenobiotics throughout the world. Exposure to caffeine occurs principally via diet, as well as pharmaceutical products. CYP1A2 mediates more than 95% of caffeine metabolism. CYP1A2 is among the isoenzymes with pronounced interindividual variation in activity caused by constitutional and environmental factors [9].

In this present study, we hypothesized that the ingestion of menthol would modify the metabolism of caffeine. If menthol inhibits caffeine metabolism, it would result in decreased clearance and higher plasma levels of caffeine. Therefore, subjects might experience increased cardiovascular and central nervous system side effects when consuming caffeine. We used caffeine to study the effects of menthol on drug metabolism—because of widespread exposure of people to caffeine per se and its use as a substrate probe for the investigation of CYP1A2 enzyme activity [10]. The interaction between menthol and caffeine has not, to our knowledge, previously been studied in man. Because of the potential for pharmacokinetic and pharmacodynamic interactions and because co-administration of these two food constituents can be expected, a study of the effect of menthol on the action of caffeine was performed.

Materials and methods

Subjects

Eleven female subjects aged from 18 years to 50 years (mean ± SD 29 ± 9.7 years) were included in this study. Their body weight ranged 50.0 kg to 62.0 kg (mean 53.7 ± 3.3 kg) and their height ranged 150 cm to 170 cm (mean 161.7 ± 4.9 cm). They were either fellows of the Pharmacology Department of Dokuz Eylul University Medical Faculty or their friends. Since we wanted to exclude the effects of gender on CYP1A2 activity, female subjects were selected [11]. The subjects were in good health on the basis of medical history, and routine biochemical and hematology testing. They were non-smokers and were not taking medications, including oral contraceptives. During the study (2 days before and 24 h after the procedure), the subjects were instructed to avoid any food or drink containing caffeine or menthol. The study protocol was approved by the Ethics Committee of Dokuz Eylul University Hospital, and each subject gave her written informed consent before the study.

Chemicals

Caffeine and menthol were obtained from Sigma (Caffeine Anhydrous, Sigma-Aldrich Chemie Gmbh, Steinheim, Germany), Mallinckrodt Baker (Menthol USP, Mallinckrodt Baker Inc. Paris, Kentucky), respectively. Gelatin capsules were filled with an appropriate dose of menthol or glucose (placebo) in the investigator's laboratory. Coffee was prepared by adding 200 mg anhydrous caffeine to decaffeinated instant coffee (Nescafe Classic, decaffeinated, Nestlé Espana S.A.) with 150 ml of water. Decaffeinated coffee (1.5 g; measured caffeine content 13.9 ± 1.7 μg/ml) was used per glass of coffee.

Study design

This was, a randomized, cross-over, double-blind study, with two phases separated by at least 1-week washout period. After an overnight fast, at 0800 hours, each subject consumed a single oral dose of 100 mg menthol or placebo capsules with 100 ml of water and 150 ml coffee containing 200 mg caffeine within 5 min.

Blood samples (8 ml each) were withdrawn through an indwelling intravenous cannula before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 h after; and via venipuncture at 24 h after administration of menthol or placebo capsules and coffee. Serum samples were separated by centrifugation at 2050 *g* for 15 min within 3 h of collection. Aliquots of serum were stored at −20°C until analysis of caffeine concentrations.

Measurement of systolic and diastolic blood pressures (BP) and heart rate (HR) were taken immediately before blood sampling. BP and HR were measured using an automatic monitor (Patient Monitor, GH Medical, USA). These cardiovascular measurements were recorded at −15, −10, −5, 0, 10, 20, 30, 45, 60, 80, 90, 105 and 120 min after menthol or placebo capsules and coffee. Subjects were kept fasting and in a supine position for the duration of the 120-min study. The morning baseline values were measured after 20 min of rest in the supine position.

The subjective effects were studied using an eight-item questionnaire. The questionnaire was given five times (at −10, 15, 40, 65, 80 min) during the first 120 min. The subjects were asked the following questions: (1) how strong is the coffee? (2) how much do you like the effect? (3) do you feel nauseated? (4) do you feel dizzy or lightheaded? (5) do you feel stimulated? (6) do you feel heartburn or stomach discomfort? (7) do you feel flushing or warmth in the skin? (8) do you feel fast heart beating or palpitations? The questions were rated on a 10-cm visual analog scale with labeled 0 (not at all) and 10 (extremely).

Analytical chemistry

The extraction of caffeine from serum was carried out using a previously described method by Jacob et al. [12]. Sample analysis was performed using GC-MS (Hewlet Packard 6890 GC, 5973 MSD). High-performance capillary column (crosslinked 5% PH ME siloxane), with dimensions of 30 m × 0.25 mm × 0.25 μm, was used for separation. Injections (1 μl) were made in the splitless mode with an injection port temperature of 250°C, the carrier gas (helium) flow rate was 1 ml/min and septum purge on-time was 1 min. The temperature programmed from 70°C to 115°C at 60°C/min, then held for 4 min at 115°C, from 115°C to 150°C at 7°C/min and from 150°C to 270°C at 25°C/min. The temperature of the transfer line to the mass spectrometer was set at 280°C. Electron multiplier was programmed to carry out analysis at 200 V above the autotune value. Ionization was in the electron impact (EI) mode at 70 eV. 1,3-(15 N)-2-(13C)-Caffeine was used as an internal standard (a gift from Dr Peyton Jacob, Clinical Pharmacology Laboratory, University of California, SF).

Calibration was performed with aqueous solution at concentrations 0, 500, 1000, 2000, 3000, 4000 and 5000 ng/ml for caffeine. The internal standard concentration was 1000 ng/ml. The relationship between response and analyte concentration was linear in the considered calibration range ($r^2 = 1$). The ions (m/z) used for quantification were 194 for caffeine and 197 for internal standard with retention time of 13.40 min. The lower limit of quantification

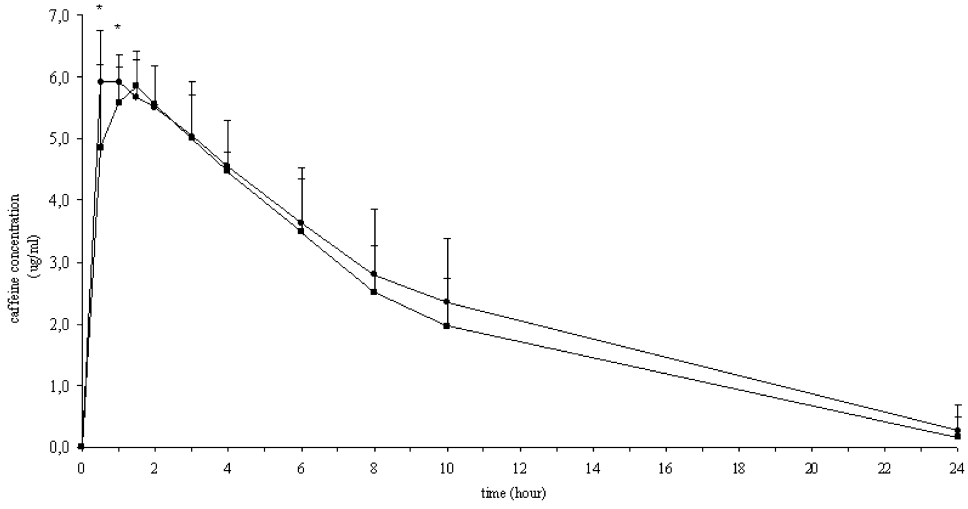

Fig. 1 Mean (SD) serum caffeine concentration–time curve, after 200 mg caffeine in coffee in the presence of 100 mg menthol or placebo. Placebo *circles*, menthol *squares* ($n = 11$). *Phase difference $P < 0.05$, caffeine with menthol versus caffeine with placebo at 0.5 h and 1 h

for caffeine was 10 ng/ml. The interday coefficient of variation for standard aqueous solution of caffeine concentration at 2000 ng/ml was 6.1% ($n = 36$). The intraday coefficients of variations for standard aqueous solution of caffeine concentrations at 500, 2000, 5000 ng/ml were 4.5%; 3.7% and 6.2%; respectively ($n = 5$). Each plasma sample was measured in duplicate. The respective mean values were used for further calculations.

The assay was controlled for possible physicochemical interaction of caffeine with menthol and decaffeinated coffee. For this purpose, an in vitro study was conducted. Briefly, 1.33 mg caffeine dissolved in 10 ml water was mixed with 0.66 mg menthol, 10 mg decaffeinated coffee or both. The samples were visually inspected and analyzed for caffeine by the above-described GC-MS method.

Data analysis

Caffeine kinetics were characterized by the area under the plasma concentration–time curve $(AUC)_{0-24}$, and $(AUC)_{0-\infty}$, peak concentration in serum (C_{max}), time to reach C_{max} (t_{max}), and terminal half-life ($t_{1/2}$). C_{max} and t_{max} were determined from the actual measurements. The elimination rate constant k_e was estimated using at least four data points of the terminal phase (from 4 h to 24 h) of the log serum caffeine concentration–time curve. The elimination half-life was obtained from $t_{1/2} = 0.693/k_e$. $(AUC)_{0-24}$ and $(AUC)_{0-\infty}$ were calculated using the trapezoidal rule. $(AUC)_{0-\infty}$ was estimated by the addition of the residual area beyond the sampling time of the last measurable concentration. The residual area was calculated from integration on the basis of the regression slope of terminal elimination phase. The oral clearance (CL_{oral}) of caffeine was calculated as the dose divided by the $(AUC)_{0-\infty}$.

Individual time profiles of cardiovascular effects were calculated on the basis of change from the morning baseline value. The effect area during the first 120 min following menthol/placebo capsule and coffee ingestion, $(AUEC)_{0-120}$, was calculated using the linear trapezoidal method.

Statistical analysis

Differences in pharmacokinetic and pharmacodynamic parameters for caffeine after co-administration with menthol or placebo capsule were analyzed by the paired Student *t*-test. In addition, to examine drug reactions as a bioequivalence problem, the ratio of pharmacokinetic parameters in the menthol relative to placebo conditions was determined, along with the 95% confidence intervals [13]. Cardiovascular data and subjective questionnaire at various times were analyzed by repeated-measures ANOVA. Statistical calculations were performed using the Instat program (GraphPAD Software, San Diego, CA, USA). The differences were considered statistically significant when P was < 0.05. Data are presented as mean values with SD.

Results

Serum caffeine concentration–time curves were plotted for each subject, and pharmacokinetic parameters were calculated. The mean serum concentration–time profiles after ingestion of 200 mg caffeine with menthol or placebo capsules are shown in Fig. 1. The $(AUC)_{0-24}$ and $(AUC)_{0-\infty}$ values of caffeine were not significantly different during the menthol and placebo phases. Menthol had a highly significant effect on caffeine t_{max}. Caffeine t_{max} value was 1.8-fold longer during menthol phase. The C_{max} values of caffeine were lower during menthol phase than placebo phase, but the difference was not significant ($P = 0.065$). However, serum levels of caffeine were significantly lower at 0.5 h ($P = 0.003$) and 1.0 h ($P = 0.02$) during the menthol than the placebo phase. Pharmacokinetic parameters of caffeine are summarized in Table 1. The ratios of menthol/placebo values for selected pharmacokinetic parameters with 95% confidence intervals are as follows: $t_{max} = 1.19$ (95% CI 1.37–2.44); $C_{max} = 0.95$ (0.90–1.00); $t_{1/2} = 1.05$ (0.84–1.26); and $AUC_{0-24} = 0.95$ (0.85–1.05). The 95% confidence intervals of the ratios of t_{max} in the menthol versus placebo condition did not overlap 1.0, consistent with the findings of significant difference with the paired *t*-test. Analysis of plasma samples taken just before caffeine administration (0 h) verified the absence of residual caffeine. This indicates that there were no carryover effects of caffeine.

Cardiovascular data from nine subjects were analyzed because the cardiovascular data of two subjects were lost due to technical reasons. The average baseline HR was 74 beats/min in the placebo phase and 70 beats/min in the menthol phase (NS). After caffeine, HR decreased in both treatment phases. The maximum decrease in HR was less in the menthol phase

Table 1 The pharmacokinetic parameters of caffeine (single oral dose, 200 mg) in combination with either menthol (**M**; single oral dose, 100 mg) or placebo capsule (**P**) in 11 female subjects. t_{max} time after dosing to maximum serum concentration, C_{max} maximum serum concentration achieved after a single oral dose, $t_{1/2}$ elimination half-life, AUC area under the serum concentration versus time curve, CL/F oral clearance

Subject no	t_{max} (min)		C_{max} (μg/ml)		$t_{1/2}$ (h)		$AUC_{(0-24)}$ (μg min/ml)		$AUC_{(0-\infty)}$ (μg min/ml)		CL/F (ml/min kg)	
	P	M	P	M	P	M	P	M	P	M	P	M
1	60	90	6.30	5.90	6.06	7.62	3587.8	3988.7	3849.9	4516.2	0.96	0.82
2	30	60	6.10	6.18	3.42	4.36	2870.8	2644.9	2900.3	2715.4	1.30	1.39
3	30	60	5.75	5.45	2.89	3.66	1906.4	2127.8	1920.4	2157.9	1.93	1.72
4	30	90	6.90	5.91	4.54	4.31	2662.0	2708.1	2740.7	2777.2	1.40	1.38
5	60	90	5.60	5.05	2.77	3.78	2430.3	2068.2	2438.8	2096.9	1.58	1.83
6	30	90	6.50	5.36	4.75	3.74	2524.8	2374.2	2609.1	2410.6	1.24	1.34
7	30	30	6.34	6.24	3.44	5.24	3081.2	3352.5	3113.4	3521.7	1.26	1.11
8	30	90	6.72	6.71	8.65	7.20	5422.5	4268.4	6445.5	4767.1	0.54	0.74
9	30	30	6.24	6.60	4.07	4.26	2587.5	2532.0	2642.2	2591.8	1.43	1.46
10	60	120	6.08	5.56	5.10	3.03	3603.5	2712.2	3770.9	2728.8	0.98	1.38
11	90	90	6.60	6.85	5.38	3.32	4269.9	3717.7	4504.2	3749.9	0.89	1.07
Mean	43.6*	76.4	6.28	5.98	4.64	4.59	3176.9	2954.1	3357.7	3093.9	1.23	1.29
SD	20.6	28.0	0.39	0.59	1.7	1.5	995.0	757.4	1260.7	916.6	0.37	0.34

*Phase difference $P < 0.05$, caffeine with menthol versus caffeine with placebo

(−8.9 ± 3.9 beats/min) than in the placebo phase (−13.1 ± 2.1 beats/min; $P = 0.024$). The maximal changes were recorded at 37.2 ± 19.5 min in the menthol phase and at 43.9 ± 33 min in the placebo phase. The mean change in HR between two phases was statistically significant at 10 min. There was no significant difference between area under the Δheart rate–time response curves for the two treatments. The mean systolic BPs at baseline were 111.2 mmHg in the placebo phase and 111.1 mmHg in the menthol phase; and the mean diastolic BPs were 67.5 mmHg in the placebo phase and 66.3 mmHg in the menthol phase. There were no significant differences in blood pressures and area under the Δblood pressure–time response curves for the two treatments. Figure 2A shows the mean HR change; Fig 2B shows the mean systolic BP change; Fig 2C shows the mean diastolic BP change.

Subjects reported significantly more heartburn or stomach discomfort with menthol capsule than with placebo capsule on the 15th, 40th and 65th minutes ($P = 0.0156$). There were no significant differences in other subjective reports comparing menthol and placebo phases.

In vitro, there was no dissolution problem of caffeine when menthol or decaffeinated coffee or both of them were added to the solution. Caffeine concentrations were similar within the three groups.

Discussion

The present study was undertaken to determine whether menthol affects the metabolism of and/or pharmacological responses to caffeine in people. Because of the potential for pharmacokinetic interactions between dietary caffeine and medications, many studies have addressed this problem. However, we are unaware of other studies of interactions between food and caffeine. Menthol is used in a wide range of products, as well as for medicinal purposes [2].

Menthol is highly lipid soluble and is rapidly absorbed from the small intestine when taken orally. We chose to use a 100-mg menthol dose in this study because, in our previous study, we had determined the disposition kinetics of this dose of menthol [14]. It was a safe dose for the subjects and was not so large as to be irrelevant with respect to exposure in the diet.

Oral absorption of caffeine is rapid and complete [9]. In humans, peak plasma concentrations of caffeine are observed approximately 30–60 min after oral consumption, although the range can be as wide as 15–120 min because of variations in gastric emptying [15]. The t_{max} value after 100 mg menthol averaged 61 ± 26 min (range 30–120 min) [14] and was close to caffeine's t_{max} value. In the present study, co-administration of menthol caused a significant increase in caffeine t_{max} and slight decrease of caffeine C_{max}, but did not affect $t_{1/2}$. These findings suggested that the effect of menthol is primarily to slow caffeine absorption.

Peppermint oil and menthol are carminative and gastric sedative, which relax gastrointestinal muscle both in vitro and in vivo [16, 17, 18, 19]. Using a receptor binding assay, Hawthorn et al. [20] demonstrated competitive antagonism with L-menthol of [^{3}H]-nitrendipine and the dihydropyridine radioligand [^{3}H]-(+)-PN200–110 binding to cardiac, neuronal and intestinal smooth muscle. L-Menthol's effect was more potent in intestinal smooth muscle than cardiac muscle and neuronal preparations. These data suggest that menthol acts by reducing the availability of calcium in gastrointestinal smooth muscle. The relaxant effect of menthol on the gastrointestinal tract could influence the rate of drug

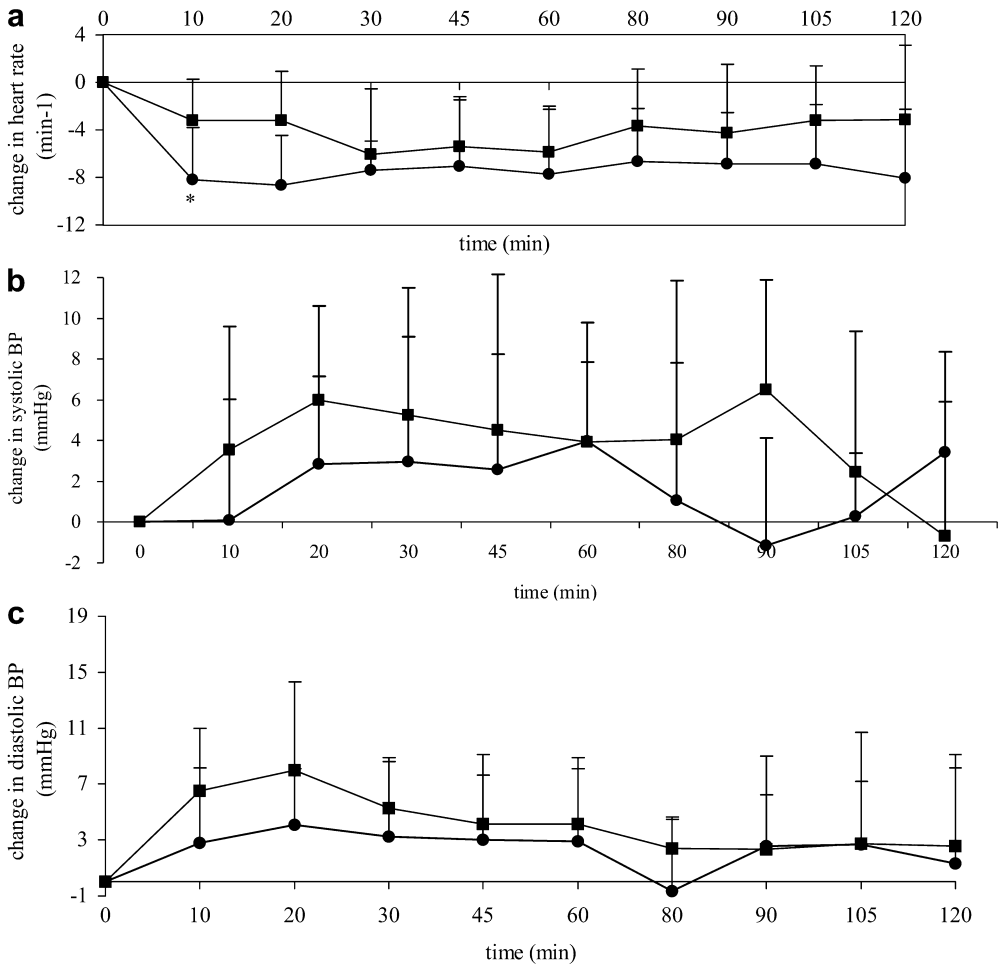

Fig. 2 Changes in heart rate (**A**), systolic blood pressure (**B**) and diastolic blood pressure (**C**) plotted over time after 200 mg caffeine in coffee in the presence of 100 mg menthol or placebo. *Data points* represent the mean (SD). Placebo *circles*, menthol *squares* ($n = 9$). *Phase difference $P < 0.05$, caffeine with menthol versus caffeine with placebo at 10 min

absorption by decreasing gastric emptying, which most likely accounts for the slowing of caffeine absorption in our study.

We obtained t_{max} and C_{max} values from the serum concentration–time curves. We took the blood samples every half-an-hour around the expected C_{max} of caffeine. Thus, we may have missed the actual peak. In vitro, the solubility of caffeine did not decrease when menthol and/or decaffeinated coffee was added. Therefore, altered solubility appears not to be responsible for the apparent delay in absorption of caffeine.

Studies in laboratory animals have found that a number of terpenoids and essential oils, many of which are used in pharmaceutical preparations and as constituents of food, induce drug-metabolizing activities of the liver and thus could modify pharmacological responses to various drugs [5]. Oral administration of L-menthol to rats (800 mg/kg per day, for up to 7 days) induces the liver microsomal enzymes cytochrome P_{450} and NADPH-cytochrome c reductase [5]. Similar observations have been made for pulegone and 1,8-cineol, in which exposure of rats to these compounds resulted in induction in the levels of cytochrome P_{450} [21, 22]. De-Olivera et al. [6] showed the weak inhibitory effect of menthol on methoxyresorufin-O-demethylase (MROD, CYP1A2) activity. In their study, 40 μM menthol decreased rate of *O*-dealkylation by 20%. However, this in vitro finding may not be extrapolated to in vivo results, because menthol is rapidly but incompletely metabolized to menthol glucuronide in vivo and the remainder of menthol is metabolized by hydroxylation [23, 24]. When human subjects were given oral doses of 100 mg menthol, only menthol glucuronide was detected in their plasma [14]. The major pathway in caffeine metabolism is N-demethylation, which is carried out by CYP1A2. Measures of caffeine N-demethylation have been used to asses hepatic CYP1A2 activity [25]. A limitation of this study is that ratios of metabolites of caffeine in urine were not measured. However, correlation between several urine metabolite ratios reflecting CYP1A2 activity and the clearance of caffeine have been observed [25]. We calculated oral clearance of caffeine, which reflects change in metabolism and did not find any difference between menthol and placebo phases. So, we conclude that ingestion of single, 100 mg menthol does not affect caffeine metabolism.

In doses typically found in two cups of coffee, caffeine causes a slight decrease in heart rate with an increase in blood pressure and systemic release of epinephrine, norepinephrine and renin [9, 26, 27, 28]. Caffeine changed blood pressure and heart rate slightly in our study. The maximal decrease in heart rate after caffeine was

significantly less in the presence of menthol. We believe that this effect of menthol can be explained in two ways: (1) menthol's effect on lowering serum caffeine levels during the absorption phase, as evidenced by this current study and (2) menthol's effect on increasing heart rate as shown in our previous study [14]. The effect of menthol to increase heart rate does not appear to be a reflex response to systemic vasodilation, since blood pressure was not lowered by menthol. The mechanism by which menthol increases heart rate has not yet been established. Of note is that Pritchard et al. [29] have found that denicotinized menthol smokers had a greater increase in heart rate following smoking than did denicotinized non-menthol smokers, supporting the idea that menthol increases heart rate.

In conclusion, we found that pure menthol (single dose administration, 100 mg) delays caffeine absorption and blunts the heart-rate slowing effect of caffeine, but does not affect caffeine metabolism. Further research is required to see whether repeated doses of menthol would affect caffeine metabolism. The possibility that menthol slows the absorption of other drugs should be considered.

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