Plasma-Kinetic Characteristics of Purified and Isolated Green Tea Catechin *Epigallocatechin Gallate* (EGCG) after 10 Days Repeated Dosing in Healthy Volunteers

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Abstract: This randomized, double-blind, placebo-controlled study assessed the safety, tolerability, and plasma-kinetic behavior of 94% pure crystalline *epigallocatechin gallate* (EGCG) after ten days' repeated dosing in 36 healthy male volunteers. Each of the three treatment groups consisted of 12 subjects; nine of them received oral EGCG in one dose of 200, 400, or 800 mg daily, and three received a placebo. Blood samples for plasma-kinetic EGCG characterization were taken on day 1 and day 10. Kinetic parameters for rate and extent, elimination half-lives, and accumulation factor (R) were determined and compared between day 1 and day 10 for each dosage group.

Orally administered EGCG is rapidly absorbed from the gut. Dose linearity was applied for single-dose application (day 1). After repeated dosing (day 10) dose linearity was applied between the 200 mg and 400 mg group. Dose escalation to 800 mg was more than dose-proportional in rate and extent, and statistically different from the 200 mg and 400 mg group. An increase in elimination half-life ($t_{1/2,z}$) and in the accumulation factor (R) in the 800 mg dosage group indicates dose-dependent saturation of capacity-limited excretion routes or an increase of hepato-duodenal re-circulation. Ten days' repeated administration of oral doses of EGCG of up to 800 mg per day were found to be safe and very well tolerated.

Key words: Green tea, catechins, *epigallocatechin gallate,* EGCG, healthy volunteers, human-kinetic, pharmacokinetics, repeated dosing

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Introduction

Green tea and green tea catechins are widely considered to be beneficial to health. In the traditional medicine of the Asia-Pacific area, green tea is recognized as a mild excitant, central nervous stimulant, diuretic, cardiotonic, and astringent. Within traditional Chinese medicine in particular, green tea is used for treating flatulence, regulating body temperature, easing digestion, and sharpening mental processes. Most of the therapeutic benefits of green tea are attributed to the catechins – polyphenols with a flavonoid structure. The catechins represent 30–40% of the total green-tea solids, and a cup of green tea typically contains between 300 mg and 400 mg polyphenols, of which 20–50 mg is *Epigallocatechin gallate* [1].

Several mechanisms by which EGCG may benefit human health have been identified. For example, EGCG has been shown to reduce fat absorption and decrease plasma cholesterol, triacylglycerols, and the ratio of low-density lipoproteins (LDLs) to high-density lipoproteins (HDLs) in animal experiments [2–4]. Epidemiological investigation in Japanese men showed a significant inverse association between the amount of green tea consumed and the total and LDL cholesterol levels [5–7]. Furthermore, EGCG may inhibit vascular smooth-muscle proliferation and platelet aggregation [8–10]. Green tea and EGCG have also been reported to increase thermogenesis and to promote fat oxidation in animals and humans [11–13]. EGCG has antioxidant properties that inhibit lipid peroxidation and atherosclerotic plaque formation, and which could provide an indirect mechanism to help maintain cardiovascular health [14–16]. The antioxidant action of EGCG and of other green tea constituents has been examined in many studies, and its role in preventing disease has been reviewed by Weisburger [17].

Green tea extracts used for studying the effects on health of catechins have varied considerably in their EGCG content. Roche Vitamins has developed a method of purifying EGCG from green tea extracts and can produce batches with a constant concentration of 94% crystalline bulk EGCG. This enables the manufacture of hard-gelatin capsules with a defined and stable EGCG content for use in controlled clinical studies to investigate the biological effects of isolated EGCG. To assess the safety and tolerability of EGCG, a previous single ascending dose study was performed in healthy volunteers and was reported elsewhere [18]. The study reported here describes the next step in determining the plasma-kinetic response to EGCG, in which separate groups of volunteers were given repeated doses of the compound at a range of concentrations to assess the dose response. The primary objective was to establish safety and tolerance aspects of EGCG administration at levels that are in excess of average dietary intake.

Methods

Ethics

This study was conducted at the PAREXEL-CEMAF Clinical Department, Poitiers, France in accordance with the revised Declaration of Helsinki 2000, the French Huriet's Law, and the rules of International Conference on Harmonization Good Clinical Practice (ICH GCP). EGCG trial supplies were manufactured and blister-packed according to good manufacturing practice (GMP) regulations and the EGCG analytical determinations were performed under documented good laboratory practice (GLP) requirements. The study protocol and the procedure for informed consent were approved by the ethics committee of the Poitou-Charentes region (Comité Consultatif de Protection des Personnes qui se prêtent à la Recherche Biomédicale). Each volunteer received written and verbal information and gave written informed consent to participate in this trial before the first treatment.

Subjects

Inclusion Criteria

Healthy, male Caucasian volunteers were selected to participate in this study. Age range for study inclusion was 18–45 years, and the Lorentz Index [= height – 100 – (height – 150) / 4] had to be within 15% of reference value. The term "healthy" was defined as "no clinically relevant deviations from normal" and was assessed by medical examinations and history, clinical laboratory testing (including negative results for HIV, hepatitis, and drug abuse screening) and vital signs measurement. A summary of the descriptive data of the study population is provided in Table I. There were no relevant differences between the different treatment groups with regard to average demographic characteristics. All the subjects were non-smokers, covered by French Social Security, and were willing and able to give informed consent, to understand and to comply with the study requirements.

Exclusion Criteria

Subjects were excluded from study participation if they had a history of specific hypersensitivity to common drugs or to EGCG or EGCG-containing foodstuff, beverages, or cosmetics, or had taken medication 14 days before the study began. Other exclusion criteria included: history of relevant gastrointestinal, liver, or kidney diseases, gastrointestinal surgery, metabolic diseases, or any other condition that was likely to interfere with the absorption, metabolism or excretion of EGCG. Subjects were not considered for this study if they were participating in or had participated in another clinical study in the three months

Table I: Demographic data summary

Parameter	Statistics	All Subjects	200 mg EGCG	400 mg EGCG	800 mg EGCG	Placebo
Age (years)	N	36	9	9	9	9
	Mean	28.94	28.67	28.78	27.11	31.22
	SD	5.37	6.30	2.64	5.71	6.10
Weight (kg)	N	36	9	9	9	9
	Mean	72.88	71.67	71.94	70.67	77.22
	SD	8.41	8.41	8.72	8.46	7.85
Height (cm)	N	36	9	9	9	9
	Mean	177.97	178.22	177.11	177.67	178.89
	SD	6.03	6.42	4.94	7.66	5.71
Lorentz index (%)	N	36	9	9	9	9
	Mean	7.11	6.06	7.39	7.73	7.24
	SD	4.29	4.83	3.86	4.26	4.74

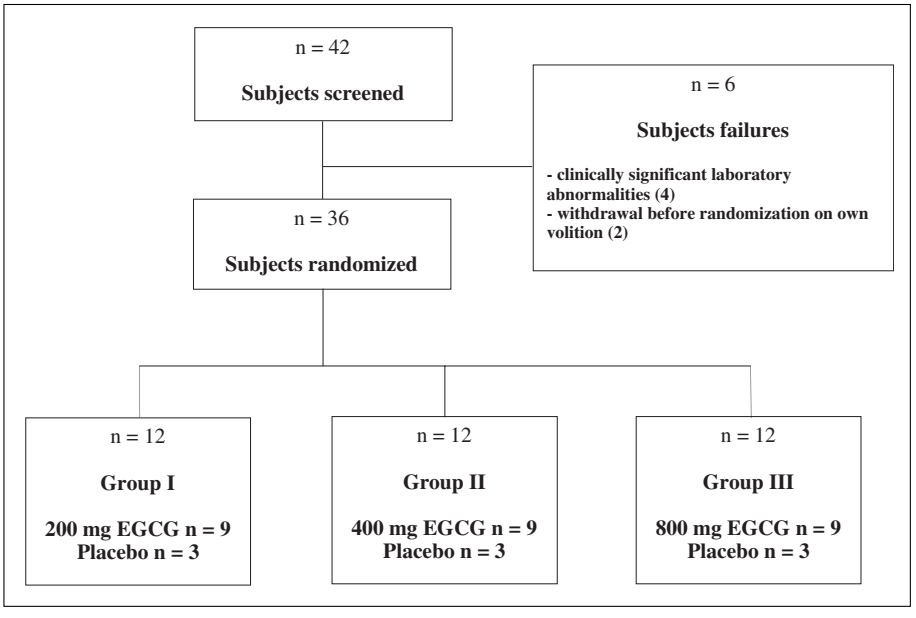

Figure 1: Flow chart of subject's disposition.

prior to study initiation; had donated blood in the 90 days prior to the start of the clinical study; had had a general anesthetic in the 30 days prior to the start of the clinical study; or had taken enzymatic inductors or inhibitors in the three months prior to the study. Subjects were excluded during the study if they: took medicinal drugs in addition to the study substance (except for the treatment of adverse events); failed to comply with the study protocol; or tested positive for drugs (urine) or alcohol (blood).

Study Design

This clinical study was single-center, randomized, placebo-controlled, and double-blinded. 36 volunteers were divided into three groups of 12 people, nine of whom received EGCG at a single concentration and three the placebo. Investigations with each group were carried out in a sequential manner, increasing the dose of EGCG at each iteration. The starting dose was 200 mg, the interim dose 400 mg, and the maximum dose 800 mg. Administration of EGCG took place over ten continuous study days (study days 1 to 10); daily in the morning after fasting overnight. Volunteers were exposed once to EGCG and baseline levels of the compound were otherwise undetectable.

Assessment Procedures

After screening for eligibility for the study, the general state of health of the subjects was checked again using a series of questions and, where necessary, by further phys-

ical examination immediately prior to administration of the medication. Special care was taken to ensure that no drugs, nonprescription products, or dietary supplements were ingested during the period between the screening examination and the first investigation day. During the treatment periods, subjects were confined to the Clinical Department of PAREXEL-CEMAF from Day 1 (6:00 p.m.) until after the follow-up examination on the morning of Day 11 (at about 10:00 a.m.). Total duration of confinement per subject was 11 nights and 11 days. Post-study medical examinations were performed within 26 hours after the last dose of EGCG. After each dose level a tolerability evaluation was made. Progression to the next dose level was allowed only if the previous dose was well tolerated.

During the in-house period the subjects were not allowed to leave the study site. All foods and beverages were provided only at the study catering facility and were free of EGCG and alcohol. The EGCG capsules were taken orally in the morning in a standing position with 400 mL of tap water under medical supervision after a minimum 10-hour abstinence from food. The time of taking the EGCG capsules was defined as T_0 for the determination of the plasma kinetic profile. First food intake (standardized breakfast) was allowed after four hours. On study days 1 and 10, blood samples for plasma kinetic analysis were taken pre-dose and at 0.5 h, 1 h, 1.5 h, 2 h, 2.5 h, 3 h, 5 h, 8 h, 12 h, 16 h, 22 h, and 24 h after T_0. Samples were centrifuged and stored at –80°C pending analysis. The study was regularly monitored by the Roche Vitamins study monitor and audited by the Quality Assurance Unit of PAREXEL-CEMAF. Trial supplies were hard-gelatin capsules each containing 50 mg of EGCG, and were produced, blister-packed, and quality controlled by PCI, Clinical Services, Schorndorf, Germany and PCI, Westhoughton, UK.

Safety Parameters

Tolerability of EGCG was assessed during the whole study period at reasonable time intervals. Volunteers were encouraged to report adverse events and clinical safety parameters were determined at screening, study day –1 and within 24 hours after the last dosing: clinical laboratory (red blood cells, hemoglobin, hematocrit, platelets, leukocytes, prothrombin rate, activated partial thromboplastin time, creatinine, ALT, AST, γ-GT, glucose, total proteins, urea, total and conjugated bilirubin, alkaline phosphatases, LDH, ionogram, total cholesterol, HDL, LDL, triglycerides, and urine analysis), vital signs (blood pressure, heart rate, and ECG) and physical examination.

As there is evidence from some animal experiments that chronic exposure to tea catechins could potentially lower the plasma concentrations of fat-soluble vitamins, the effect of EGCG on the plasma concentrations of vitamins A, C, E, and β-carotene were additionally determined [19, 20].

EGCG Plasma Concentrations

An original, sensitive, and specific assay was developed and validated for the determination of EGCG in human plasma. The compounds and the internal standard (propyl gallate) were separated from the plasma by solid-liquid extraction and the samples analyzed by liquid chromatography/tandem mass spectrometry (LC/MS/MS) in atmosphere-pressure chemical ionization (APCI) positive mode. Liquid chromatography was performed using an HP 1100 system from Agilent Technologies (Palo Alto, USA). The high-pressure liquid chromatography (HPLC) device was connected to a MDS SCIEX API 3000 (Concord, Canada) system operating in the Turbo Ion Spray negative mode. The MS/MS system was used in multiple reaction monitoring mode to monitor predefined ion transitions. *Free* EGCG was defined as unconjugated EGCG and *total* EGCG as the sum of both, conjugated and unconjugated EGCG. *Total* EGCG was quantified after hydrolysis of its esters with β-glucuronidase X-A 200,000 IU (from *Helix pomatia;* Sigma, USA) and sulfatase VIII 500 IU (from abalone; Sigma, USA). The lower limit of quantification was 5.0 ng/mL. The assay was performed using 200 µL of human plasma. Concentrations were expressed as nanograms compound per milliliter of human plasma.

Plasma-Kinetic Parameters

EGCG plasma-kinetic characteristics were assessed by using the following variables: maximum (C_{max}) and minimum (C_{min}) plasma concentrations as well as the time to reach C_{max} (T_{max}) were read directly from the observed concentrations. Non-linear regression of a single ($Ce^{-Kel.t}$) exponential function in the terminal phase of the (untransformed) plasma concentration (C) versus time (t) profile, where Kel is the terminal rate constant, was performed using the method of non-linear least squares to calculate the apparent terminal elimination half-life ($t_{1/2z}$) = (ln 2)/Kel = 0.693/Kel. The area under the plasma concentration versus time-data pairs ($AUC_{(0\text{-}t)}$) was calculated according to the linear trapezoidal rule from 0 h to the last quantifiable concentration after drug administration. The area under the curve from 0 h to infinity was extrapolated from $AUC_{(0\text{-}t)}$ by adding $C(t)/K$el. Thus, $AUC_{(0\text{-}\infty)} = AUC_{(0\text{-}t)} + C(t)/K$el, where $C(t)$ is the last quantifiable concentration. Accumulation factor R was calculated by

$$\frac{AUC(0\text{–}\tau)day10}{AUC(0\text{–}\tau)day1}.$$

Through values were taken immediately before the dosing [21–23].

Non-compartmental plasma kinetic analysis was performed by the Department of Pharmacokinetics of PAREXEL-CEMAF using Kinetica™ (version 3.0) software. The non-linear regressions to determine the terminal half-lives were performed using PKCalc, a program developed in the Biometry Division of FARMOVS-PAREXEL and written in Delphi 3. This program has been fully validated against WinNonlin®. Statistical analyses, the calculation of descriptive statistics, and the production of the graphs of the plasma kinetic data were performed by the biostatistical unit of PAREXEL-CEMAF using SAS® software version 6.12 (Statistical Analysis System, SAS Institute, North Carolina, USA) under Windows NT [23, 24]. Kinetic analysis was performed on those randomized subjects who received the study drug and completed the study according to the protocol (per-protocol analysis). Safety analysis was performed on all the randomized subjects including those receiving placebo (intention-to-treat analysis) [23].

Results

The results of the plasma-kinetic evaluation are presented in Table II for EGCG *total* form and in Table III for EGCG *free* form. Mean plasma concentration time-course profiles for EGCG *total* form for each dosage group comparing study day 1 versus study day 10 are given in Figure 2.

To facilitate the estimation of dose proportionality, dose-normalized rate ($C_{max,norm}$) and extent parameters ($AUC_{(0-\infty),,norm}$) were calculated for each dose strength and are shown in Table IV (dose-normalized to 800 mg EGCG).

Ninety-four percent pure crystalline EGCG – in the form of hard-gelatin capsules ingested orally in fasting state – was absorbed from the intestine and appeared in blood in significant concentrations [after single dose (Day 1) and after repeated dosing (Day 10)]. Average times to reach C_{max} (T_{max}) were between 1.39 and 2.00 hours, independent of dose, time, or EGCG form (*free/total*). Despite a very high observed inter-individual variability of EGCG plasma concentrations and, consequently, highly variable plasma-kinetic parameters, it may be stated that EGCG as a single dose application (Day 1) was dose proportional

Table II: Plasma-kinetic parameters of total EGCG after 10 days repeated dosing and statistical results of ANOVA after natural log-transformed data (* = $p < 0.05$ for 400 mg vs. 200 mg, ** = $p < 0.05$ for 800 mg vs. 200 mg, *** = $p < 0.05$ for 800 mg vs. 400 mg)

200 mg EGCG Total Form								
DAY	Parameter	C_{max}	C_{min}	T_{max}	$AUC_{(0-\tau)}$	$AUC_{(0-\infty)}$	$T_{1/2.z}$	R
1	Mean	376.9	na	1.8	1403.3	1415.9	2.7	na
	SD	171.7	na	1.3	632.2	638.8	1.1	na
	n	9	–	9	9	9	9	–
10	Mean	267.9	BLQ	1.4	1123.6	1128.8	2.3	0.8
	SD	76.9	BLQ	0.45	427.5	427.6	0.8	0.3
	n	9	–	9	9	9	9	9
400 mg EGCG Total Form								
DAY	Parameter	C_{max}	C_{min}	T_{max}	$AUC_{(0-\tau)}$	$AUC_{(0-\infty)}$	$T_{1/2.z}$	R
1	Mean	525.2	na	1.4	2098.12*	2111.4*	3.0	na
	SD	183.7	na	0.5	631.1	635.7	0.8	na
	n	9	–	9	9	9	9	–
10	Mean	695.8*	6.8	1.7	2633.8*	2668.7*	4.2*	1.4
	SD	632.6	BLQ	0.7	1843.5	1854.3	1.4	1.3
	n	9	1	9	9	9	9	9
800 mg EGCG Total Form								
DAY	Parameter	C_{max}	C_{min}	T_{max}	$AUC_{(0-\tau)}$	$AUC_{(0-\infty)}$	$T_{1/2.z}$	R
1	Mean	1682.1**/***	na	1.8	5219.2**/***	5254.9**	3.4	na
	SD	996.6	na	0.8	2935.0	2955.3	0.8	na
	n	9	–	9	9	9	9	–
10	Mean	2431.4**/***	11.8	1.7	8392.5**/***	8542.9**	5.2**/***	1.9**
	SD	1221.2	7.0	0.5	3839.4	3902.0	0.8	1.2
	n	9	8	9	9	9	9	9

C_{max} in ng/mL T_{max} in hours AUC in ngxh/mL $T_{1/2.z}$ in hours R (no unit)

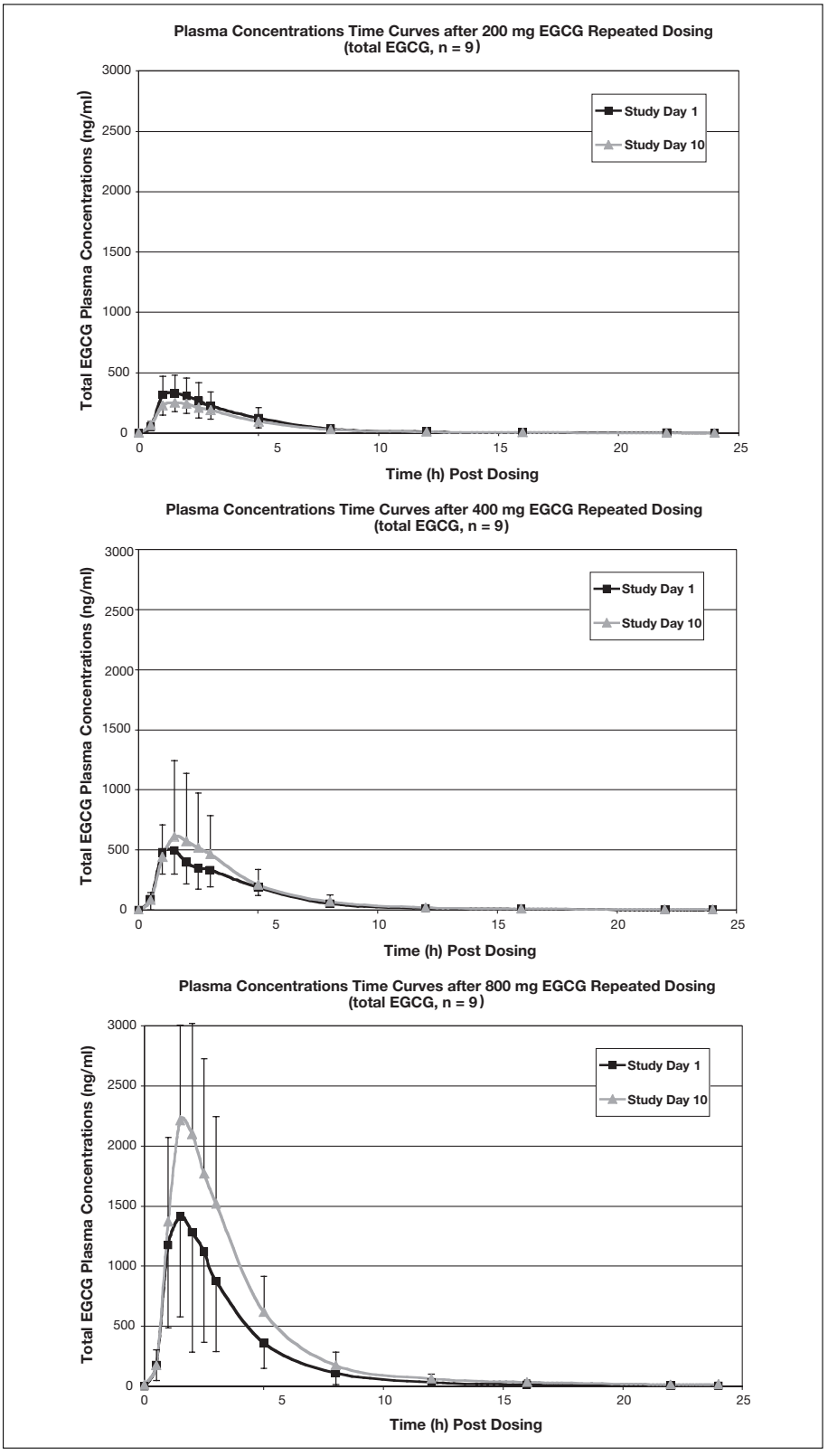

Figure 2: Mean EGCG (total) plasma concentration-time curves after repeated dosing of 200 mg, 400 mg and 800 mg EGCG comparing study day 1 versus study day 10 (± SD).

Table III: Plasma-kinetic parameters of free EGCG after 10 days repeated dosing

200 mg EGCG Free Form								
DAY	Parameter	C_{max}	C_{min}	T_{max}	$AUC_{(0-\tau)}$	$AUC_{(0-\infty)}$	$T_{1/2.z}$	R
1	Mean	327.4	na	2.0	1222.0	1192.4	2.3	na
	SD	170.2	na	1.2	425.1	444.6	0.5	na
	n	9	–	9	9	9	9	–
10	Mean	259.5	BLQ	1.6	1107.5	1078.5	2.4	0.9
	SD	63.5	BLQ	0.7	359.78	371.6	0.4	0.3
	n	9	–	9	9	9	9	9
400 mg EGCG Free Form								
DAY	Parameter	C_{max}	C_{min}	T_{max}	$AUC_{(0-\tau)}$	$AUC_{(0-\infty)}$	$T_{1/2.z}$	R
1	Mean	504.0	na	1.6	1979.9	1971.9	2.6	na
	SD	197.2	na	0.7	645.5	652.8	0.7	na
	n	9	–	9	9	9	9	–
10	Mean	704.5	6.5	1.8	2447.4	2475.2	4.1	1.5
	SD	723.7	BLQ	0.7	1851.9	1861.3	1.5	1.6
	n	9	1	9	9	9	9	9
800 mg EGCG Free Form								
DAY	Parameter	C_{max}	C_{min}	T_{max}	$AUC_{(0-\tau)}$	$AUC_{(0-\infty)}$	$T_{1/2.z}$	R
1	Mean	2268.8	na	1.9	5799.7	5840.3	4.1	na
	SD	2113.1	na	0.7	3763.2	3791.1	0.8	na
	n	9	–	9	9	9	9	–
10	Mean	2800.2	12.3	1.8	9032.1	9155.9	5.0	1.9
	SD	1552.5	6.1	0.56	4249.6	4309.7	0.7	1.2
	n				9	9	9	9

C_{max} in ng/mL T_{max} in hours AUC in ngxh/mL $T_{1/2.z}$ in hours R (no unit)

Table IV: Dose-normalized $C_{max,norm}$ and $AUC_{(0-\infty),norm}$ of EGCG total form (n = 9 in all groups, normalized to 800 mg)

200 mg EGCG Total Form			
DAY	Parameter	$C_{max,norm}$	$AUC_{(0-\infty),norm}$
1	Mean	1507.8	5663.6
	CV%	45.6	45.1
10	Mean	1072.0	4515.3
	CV%	28.7	37.9
400 mg EGCG Total Form			
DAY	Parameter	$C_{max,norm}$	$AUC_{(0-\infty),norm}$
1	Mean	1050.5	4222.8
	CV%	35.0	30.1
10	Mean	1391.6	5337.4
	CV%	91.0	69.5
800 mg EGCG Total Form			
DAY	Parameter	$C_{max,norm}$	$AUC_{(0-\infty),norm}$
1	Mean	1682.1	5254.9
	CV%	59.3	56.2
10	Mean	2431.4	8542.9
	CV%	50.2	45.7

$C_{max,norm}$ in ng/mL AUC_{norm} in ng × h/mL

Table V: Trough values for total EGCG on study days 2 to 10

Study Day	400 mg EGCG mean plasma concentrations ng/mL (± SD)	n	800 mg EGCG mean plasma concentrations ng/mL (± SD)	n
2	5.99 (1.27)	2	9.67 (3.22)	5
3	6.64 (2.27)	3	9.29 (3.62)	9
4	8.36 (0)	1	10.82 (4.45)	9
5	11.04 (0)	1	12.15 (4.76)	9
6	7.57 (3.02)	2	12.00 (3.77)	9
7	5.44 (0)	1	13.32 (5.10)	9
8	11.75 (0)	1	14.38 (6.54)	9
9	8.21 (0)	1	12.48 (5.67)	9
10	8.45 (0)	1	13.51 (6.83)	9

between 200 mg, 400 mg, and 800 mg in rate and extent (mean C_{max} (ng/mL) on Day 1 in the 200 mg group 376.9, 400 mg group 525.2, and in the 800 mg group 1682.1; mean $AUC_{(0-\infty)}$.(ng × h/mL) 1415.9, 2111.4, and 5254.9). After repeated EGCG dosing (Day 10) the dose adjustment from 200 mg up to 400 mg also followed the dose-proportional pattern, whereas the dose escalation from 200 mg to 800 mg and from 400 mg to 800 mg was more than dose-proportional (mean C_{max} (ng/mL) on Day 10 in the 200 mg group 267.9, 400 mg group 695.8, and in the 800

mg group 2431.4; mean $AUC_{(0-\infty)}$.(ng × h/mL) 1128.8, 2668.7, and 8542.9.

Elimination half-lives for EGCG *total* form were 2.7 h (200 mg), 3.0 h (400 mg), and 3.4 h (800 mg) on Day 1 and 2.3 h (200 mg), 4.2 h (400 mg), and 5.2 h (800 mg) on Day 10. While the average elimination half-life decreased after repeated dosing with 200 mg EGCG (Day 1 versus Day 10), they were prolonged with increased exposure in the 400 mg and 800 mg dose groups (dose and time). This effect was statistically insignificant between the 200 mg and 400 mg dosage group (Day 1 and Day 10) due to the very high degree of inter-individual variation. However, on study Day 10 the differences between the 200 mg (2.3 h) and 800 mg (5.2 h) groups, as well as the 400 mg (4.2 h) and 800 mg (5.2 h) dosage groups, were statistically significant. The mean Accumulation Factor (R) increased with dose escalation from 0.8 (400 mg) to 1.4 (400 mg) and 1.9 (800 mg), respectively. The difference between the 200 mg and 800 mg dose group was statistically significant ($p = 0.0123$) but it was not statistically different from one in all dosage groups, which is the more important test (Accumulation Factor = 1, means no accumulation).

Trough values were zero at all time points in the 200 mg group and nearly all in the 400 mg group. Detectable EGCG concentrations were measured only after 800 mg dosing, where minimal concentrations reflected the late stage of elimination after 24 hours (approximately 0.5 % of corresponding C_{max} values). A continuous steady state in the pharmacological sense was not reached.

Repeated dosing of 200 mg, 400 mg, or 800 mg EGCG once daily was well tolerated. No serious adverse event or any other clinically relevant adverse event was reported. Minor changes in different physiological parameters (blood pressure, ECG, blood lipids, liver enzymes, etc.) were all without clinical relevance and no consistent EGCG or dose-related effect could be demonstrated. One subject out of the 800 mg group presented with a slight and reversible increase of ALT (SGPT) (2-fold above NR at end of study and recovery within 14 days after the study). No effects of EGCG on plasma concentrations of vitamins A, C, E, and β-carotene were observed.

Discussion

Complete sets of plasma-kinetic data for 94% pure EGCG after 10 days repeated dosing in the dose groups 200 mg, 400 mg, and 800 mg were assessed. As our volunteers ingested their trial supplies after fasting overnight and remained fasting up to four hours post-dosing, any kind of food-interaction was systematically excluded. A parallel-group study design was chosen in order to increase the number of subjects who could be assessed for safety and tolerability. After single-dose application (Day 1) plasma EGCG behaved dose-proportionally in rate and extent, without significant changes in the elimination half-lives. After repeated dosing a dose-proportionality was identified between the 200 mg and 400 mg group. However, the differences in rate and especially in extent between the 200 mg/800 mg and also between the 400 mg/800 mg groups were more than dose-proportional. Interestingly, it seems that after repeated dosing with 200 mg EGCG, a certain induction of elimination pathways occurred (metabolization and/or excretion), resulting in a lower extent of systemic availability, and a reduced C_{max} and elimination half-life of EGCG. The comparison of the mean AUCs and C_{max} values of the 200 mg group showed a decrease between Day 1 and Day 10 of about 10% (*free* and *total* form). In parallel, the mean elimination half-life also decreased from 2.7 h to 2.3 h (EGCG *total* form). Because the Accumulation Factor for EGCG *total* form did not significantly differ from one, an accumulation of EGCG in the body is not to be expected for the average population.

Nevertheless, the increase of elimination half-lives suggests that EGCG excretion is a dose-dependent, capacity-limited process. Additionally, the amount of hepato-duodenal re-circulating EGCG will increase after repeated dosing, which might also contribute to the observed increase of systemic availability of EGCG. The constancy of T_{max} values across the different dosage groups and study days is a hint that no relevant changes in the absorption process occurred. As expected, the inter-individual variability in this parallel group comparison was high, which has also been reported in other human studies with EGCG [18, 25, 26].

To our knowledge, no published information is available about the plasma-kinetic characteristics of single tea catechins after repeated application over several days, determined under controlled conditions in humans. In a few articles, more or less sporadic measurements were taken without calculating essential plasma-kinetic parameters according to approved pharmaceutical standards. None of them were conducted with purified or isolated catechins. In every case, either tea, tea extracts, or special polyphenol preparations were used, consisting of multiple components [27–31]. This study demonstrated that repeated dosing of EGCG was well tolerated, even though the highest dose tested exceeded the average catechin intake of tea-drinking populations.

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