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Limited sampling estimates of epigallocatechin gallate exposures in cirrhotic and noncirrhotic patients with hepatitis C after single oral doses of green tea extract.

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**Limited Sampling Estimates of Epigallocatechin Gallate
Exposures in Cirrhotic and Non-cirrhotic Hepatitis C Subjects
After Single Oral Doses of Green Tea Extract**

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Nonstandard abbreviations: Epigallocatechin Gallate (EGCG), green tea extract (GTE), Hepatitis C Virus (HCV), Child-Pugh (CP), hepatocellular carcinoma (HCC), limited sampling strategy ($AUC_{LSS\ 0\rightarrow 10}$), Maximum plasma concentrations (C_{max}) area under the curve (AUC), liquid chromatography-mass spectrometry (LC-MS), Half-life ($t_{1/2}$)

Keywords:

Epigallocatechin-3-gallate (EGCG), Green tea extract (GTE), Hepatitis C Virus , Hepatotoxicity, Hepatocellular Carcinoma, Cirrhosis

Abstract

Background: Epigallocatechin-3-gallate (EGCG) has anti-angiogenic, anti-oxidant, and anti-fibrotic properties that may have therapeutic potential in Hepatitis C Virus (HCV) induced cirrhosis. However, cirrhosis may impact EGCG disposition and augment its reported dose-dependent hepatotoxic potential.

Objective: The safety, tolerability, and disposition of a single oral dose of EGCG in cirrhotic patients with HCV were examined in an exploratory fashion.

Methods: Eleven patients with hepatitis C and detectable viremia were enrolled. Four had cirrhosis Child-Pugh (CP) class A, four CP class B, and three were non-cirrhotic. Following a single oral dose of green tea extract 400mg containing 94% pure EGCG, blood for EGCG was ascertained at 2, 4, and 10 hours.

Results: Maximum plasma concentrations (C_{max}) and exposures (AUC) to EGCG overlapped among the three groups suggesting that the disposition of EGCG is not significantly altered in patients with cirrhosis.

Conclusions: A single 400 mg oral dose of EGCG was safe and well tolerated by all of the subjects in the study. These results provide guidance for the continued investigation of the long term safety and antitumor potential of EGCG in cirrhotic patients with HCV.

Introduction

Green tea, made from the unfermented leaves of *Camellia sinensis*, is comprised of several polyphenolic compounds (catechins) and can be concentrated into a green tea extract (GTE), which, in turn, is a common ingredient in many dietary supplements. Epigallocatechin-3-gallate (EGCG) is the most abundant and potent catechin contained within GTE, comprising typically ~40% of the total polyphenol content.¹ EGCG has antioxidant, antiviral anticarcinogenic, antimutagenic, and anti-inflammatory properties, shown in several preclinical and epidemiologic studies.²⁻⁶ Preclinical data in cell culture and animal models suggest green tea may have a role as a chemopreventative agent for many types of cancer, including hepatocellular carcinoma (HCC).⁷⁻¹⁰

After oral absorption, tea catechins undergo extensive methylation, glucuronidation, and sulfation. Rapid methylation of EGCG is catalyzed by liver cytosolic catechol-O-methyltransferase. Methylation decreases the hydrophilicity of catecholic compounds; further sulfation/glucuronidation of the methylated product is usually needed for the elimination of the product from the body.^{11,12} There has been discussion that level of methylation is influenced by polymorphisms of catechol-O-methyltransferase, but the effect of this has not yet been fully studied. Within the plasma, serum albumin contributes to transport and stabilization by directly preventing EGCG oxidation. Therefore, low serum albumin may decrease EGCG plasma levels.¹³

The safety and pharmacokinetics of EGCG in patients with cirrhosis has not been described. This may reflect concerns regarding a risk for hepatotoxicity with EGCG, especially where such risk may be unpredictable due to differences in EGCG's disposition in this patient population as a result of the underlying liver disease. Reports

of hepatitis associated with the consumption of green tea preparations have been published.¹⁴⁻¹⁶ The mechanism of the potential hepatotoxicity of GTE is unclear.¹³ However it can be hypothesized that the impact of a hepatotoxic event may be magnified in patients with preexisting liver disease as a result of alterations in pathways involved in EGCG's hepatic metabolism or excretion. Differences in the disposition of silymarin, another herbal product used by patients for the self-treatment of liver disease, has been seen in liver disease.^{17,18} Alterations in the expression of hepatobiliary transporters induced by liver disease, which may lead to differences in drug disposition, have been reported.¹⁹

The risk of hepatic decompensation as a result of drug induced liver injury is greatest in patients with cirrhosis and increases with disease progression defined by Child Pugh classification.²⁰ The main goal of this study was to estimate EGCG exposure following a single oral dose of a green tea extract highly concentrated base EGCG, using a limited pharmacokinetic sampling schedule, in Child Pugh class A and B patients, and in non-cirrhotic patients with HCV. Furthermore, this study establishes the safety and tolerability of EGCG at the dose selected and serves as rationale for larger scale dose escalation and multiple dose studies in this potentially vulnerable population.

Patients and Methods

Study Participants

Adult patients with HCV viremia, and cirrhosis status assessed by prior biopsy or imaging were recruited from Thomas Jefferson University Hepatology practice for

inclusion in the study. Exclusion criteria were prior liver transplantation, hepatocellular cancer, and current HCV treatment.

Study Protocol

This was an open label, single dose, clinical trial. The study protocol was approved by the Thomas Jefferson University Institutional Review Board and all study subjects provided written informed consent. Subjects were asked to refrain from ingestion of tea or tea containing products for 14 days prior to the day of the study. The day before the study participants were instructed to fast after midnight except for drinking water. Subjects were given a single oral dose of 400mg 94% pure EGCG (TEAVIGO[®] DSM Nutritional Products Ltd). Additional compounds within the product include non-EGCG catechins (epicatechingallate, epicatechin, catechin, gallocatechin gallate, and gallic acid) at less than 5.3%.

Patients were housed in the Clinical Research Unit (CRU) for the 10 hour duration of the study after administration of EGCG. Blood EGCG levels and safety parameters (including complete blood count, comprehensive metabolic panel, and coagulation panel) were ascertained at baseline and at 2, 4, and 10 hours post dosing. Phlebotomy was performed by venipuncture. Plasma samples were collected in BD Vacutainer[®] venous blood collection tubes and CryoVial[®] collection tubes. Using P10 pipette, 10 microliters (10 ul) of Formic Acid and P100 pipette, 30 microliters (30 ul) of Ascorbic acid solution was added for every 1 milliliter of plasma, Tubes were then inverted for 5 seconds to mix thoroughly to ensure proper stability of EGCG in plasma, Samples were then stored in a -80° freezer until analysis.

Subjects were fed 4 hours after dosing. The fasting condition and sampling times were based on previously published limited sampling strategy models which had greater predictive performance under fasting conditions and were shown to accurately predict EGCG oral clearance in healthy subjects.²¹ Follow up safety labs were drawn 8 to 15 days after dosing.

Analysis of EGCG Plasma Concentrations

Plasma samples for EGCG were analyzed using LC–MS with negative ion electrospray ionization. The assay has a detection limit of 2ng/ml and is linear in the range of 2-5000ng/ml. The accuracy for EGCG quantification was 79.8% and intra- and interday precisions were 1.7 to 7.9% and 3.7 to 9.6%, respectively.

Pharmacokinetic Analysis

Estimated area under the curve for the limited sampling strategy ($AUC_{LSS\ 0\rightarrow 10}$) was calculated with the trapezoidal rule. Half-life ($t_{1/2}$) was calculated from the measurements obtained at 4 and 10 hours post-dosing. Geometric means for AUC and $t_{1/2}$ were computed for cirrhotics and non-cirrhotic controls, along with 95% confidence intervals, but the small sample sizes precluded a direct statistical comparison. The analyses were conducted in SAS 9.3.

Results:

Eleven subjects were enrolled; four with Child-Pugh Class A, four with Child-Pugh class B, and three non-cirrhotic subjects (Table 1). The median EGCG concentrations and pharmacokinetic estimates are summarized in Table 2 and Figure 1... The C_{max} was 89 ng/ml in non-cirrhotics at 2 hours; 182 ng/ml at 2 hours in cirrhotics. The AUC increased with more advanced liver disease; that is, the exposure to EGCG was

higher in cirrhotic patients than in the noncirrhotic patients. Three patients had detectable EGCG noted on baseline EGCG concentration labs. Upon later questioning, the subjects reported tea intake (not labeled as green tea) despite being asked to refrain from tea for 14 days prior to the study day. One class B cirrhotic had highly increased EGCG concentrations at baseline that were unable to be verified; therefore, these the data from this subject were excluded from final analysis. Figure 1 shows EGCG concentration over dosing day. Of note, Child Pugh subject A3 appeared to have an exposure greater than any other subject. No drug related adverse events were reported during the study or at the follow up safety visit. Two of the four Child-Pugh Class B subjects had a rise in their total bilirubin (over 2 mg/dL) noted on follow up safety labs drawn 8 to 15 days after dosing day, although these elevations were within the patients' observed retrospective range.

Discussion:

In this study we provide the first description of EGCG pharmacokinetics in patients with chronic HCV infection. The rationale for the study is predicated upon EGCG's potential therapeutic benefit in this patient population; specifically, its antiviral and antitumor effects. However, given the hepatotoxic potential of green tea extract and the potential for augmented hepatotoxicity in patients with chronic liver disease, it is important to have established safety and tolerability, even if only at one dose, before proceeding to additional studies. While point estimates of EGCG AUC suggest systemic exposure that is higher in cirrhotics than in non-cirrhotics, the relatively small number of patients, PK collection samples, and intersubject variability suggest that the study is underpowered to

detect a true difference, should one exist. This study presents exploratory data only; future studies will need to incorporate more subjects. However, the data do provide a broad estimate of EGCG disposition in this population, and show overlap between the three study panels.

Approximately 2% of the US population is infected with HCV; cirrhosis develops in 20% of those infected and HCC develops in 25% of cirrhotics, most of whom die from their disease.^{8,22} EGCG has been found to be a potent inhibitor of HCV entry in hepatoma cell lines as well as primary human hepatocytes.^{23,24} Beyond its antiviral effect on HCV, and germane to its potential use as a chemopreventative or chemotherapeutic agent for hepatocellular cancer, recent data indicate that the receptor tyrosine kinases are one of the critical targets of EGCG to inhibit cancer cell growth. EGCG has also been shown to modulate the expression of target genes which are associated with induction of apoptosis and cell cycle arrest in cancer cells.²⁵ EGCG's chemopreventative effect has been demonstrated in human subjects with chronic hepatitis B and a very high risk of hepatocellular carcinoma.¹⁰

GTE is a common ingredient in several dietary supplements, some of which have been withdrawn from the market due to safety concerns. An example of this is *Exolise* (Arkopharma, France), a weight loss supplement containing high EGCG levels was withdrawn from the market in April 2003 due to 13 cases of attributable liver injury.²⁶ Since 1966, 216 case reports of toxicity with green tea extracts were identified by the United States Pharmacopeia, of which 34 were concerning for liver toxicity.¹³ The majority of cases present with an acute hepatocellular injury pattern and most recover with cessation of use.^{12,26,27} Based on this review, no significant safety issues were

identified that would prohibit further development of green tea extract containing dietary supplements. An idiosyncratic or an immune-allergic mechanism appears to be the likely mechanism of injury. Recent animal studies with high doses of GTE and EGCG have described dose dependent hepatotoxicity resulting in severe morbidity and mortality.²⁸ However, chronic moderate to high dose daily GTE and EGCG use in healthy human volunteers was not shown to cause severe adverse effects or impair liver function.²⁹⁻³²

Prior pharmacokinetic studies have established peak blood concentrations and exposures of EGCG associated with its safety and tolerability in healthy subjects.³⁰⁻³⁴ In a study by Chow et al., following a single 800mg dose of EGCG in five healthy volunteers, AUC (min·µg/ml) ±SD was 167.1 ± 57.0 , C_{\max} (ng/mL) was 438.5 ± 28.4 and $t_{1/2}$ (min) was 114.0 ± 33.3 .³⁵ In a multi-dose study by Chow et al., volunteers were randomly assigned to receive one of the five treatments for 4 weeks: 800 mg EGCG once/day, 400 mg EGCG twice/day, 800 mg EGCG as Polyphenon E once/day, 400 mg EGCG as Polyphenon E twice/day, or a placebo once/day (8 subjects/group). There was a >60% increase in the area under the plasma EGCG concentration-time curve after 4 weeks of green tea polyphenol treatment at a dosing schedule of 800 mg once daily. No significant changes were observed in the pharmacokinetics of EGCG after repeated green tea polyphenol treatment at a regimen of 400 mg twice daily. The described dose range, which was equivalent to 8–16 cups of green tea/day, and frequency of administration of EGCG in these study appeared to be well tolerated.³⁰ The EGCG dosing in these pharmacokinetic studies is similar to the chronic dosing studies noted above which also showed no hepatotoxicity.^{30,31}

A limited pharmacokinetic sampling schedule was employed in the current study to obtain reasonable estimates of EGCG exposure while not exposing ill subjects to excessive phlebotomy. Chow et al. employed modeling and Monte Carlo simulation to formulate a limited sampling that accurately predicted pharmacokinetic parameters following EGCG administration up to 800 mg in healthy volunteers.³⁰ Limited sampling strategies have been shown to provide estimates of EGCG exposure, within a specific dosing range, that are similar to the more dense sampling pharmacokinetic investigations.²¹

The half life estimates were unchanged across patient populations, and were similar to those noted by Chow in healthy subjects. In comparison, the point estimates of AUC_{0-10} were larger in cirrhotics compared to non-cirrhotics (1281 vs. 670 min•ng/ml), though there was significant overlap and these differences were not statistically significantly different. A limitation of this study is the fact that baseline EGCG levels were detectable in a few patients at low levels despite being asked to refrain from green tea products. These low values that did not materially impact the pharmacokinetic parameter estimation. While there was intersubject variability noted in the AUC_{0-10} value, there does appear to be suggestion of a disease severity related effect on systemic exposure at similar doses of orally administered GTE. The mechanism by which this could occur could be increased extent of absorption or enterohepatic recirculation. Alternatively, decreased total clearance would need to be paired with an increase in volume of distribution to maintain an unchanged $t_{1/2}$. The current study does not provide guidance about the mechanism by which the currently observed differences could be explained.

Conclusions:

Overall, a single 400 mg oral dose of EGCG was safe and well tolerated. However, due to our small sample size and variability in pharmacokinetic exposures, detection of exposure differences or hepatotoxicity risk between were not identified. In addition, the single dose design of our study does not allow for evaluation of dose- and time-dependent hepatotoxicity risk. Overall, the exposures observed in our study suggest that the disposition of EGCG is not significantly altered in patients with cirrhosis; chronic dosing studies should be conducted to define the safety risk in this patient population.

Given its potential role as an adjunct to HCV triple therapy and as a chemopreventative agent in the HCV cirrhotic population, our findings support the conduct of a Phase I chronic dose-escalation study and multiple dose study eventually leading to a large-scale efficacy and chemoprevention trials. In light of the hepatotoxic potential of EGCG, future studies should be limited to patients with early stage (Childs Pugh Class A) cirrhosis, who remain at risk for HCC, who are monitored carefully for early signals of hepatotoxicity.

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Conflicts of Interest:

Authors claim no conflicts of interest

References:

1. Yang, C.S. and Landau, J.M. Effects of tea consumption on nutrition and health. *J. Nutr.* 2000; 130: 2409–2412.
2. Demeule M, Michau-Levesque J, Annabi B, et al. Green Tea Catechin as Novel Antitumor and Antiangiogenic. *Curr. Med. Chem.-Anti-Cancer Agents.* 2002; 2:441-463.
3. Ahn HY, Hadizadeh KR, Seul C et al. Epigallocatechin-3gallate selectively inhibits the PDGF-BB-induced intracellular signaling transduction pathway in vascular smooth muscle cells and inhibits transformation of sis-transfected NIH 3T3 fibroblasts and human glioblastoma cells (A172). *Mol Biol Cell.* 1999; 10(4):1093-1104.
4. Sung H, Nah J, Chun S, et al. In vivo antioxidant effect of green tea. [*Eur J Clin Nutr.*](#) 2000; 54(7):527-529.
5. [Ahmad N](#), [Feyes DK](#), [Nieminen AL](#), et al. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. *J Natl Cancer Inst.* 1997; 89(24):1881-1886.
6. Bushman JL. Green tea and cancer in humans: a review of the literature. *Nutr Cancer.* 1998; 31(3):151–159.
7. Sun CL, Yuan JM, Koh WP, et al. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis.* 2006; 27(7):1310–1315.

8. Mann CD, Neal CP, Garcea G, et al. Phytochemicals as potential chemopreventative and chemotherapeutic agents in hepatocarcinogenesis. *European Journal of Cancer Prevention*. 2009; 18:13-25.
9. Lamy S, Gingras D, Beliveau R. Green Tea Catechins Inhibit Vascular Endothelial Growth Factor Receptor Phosphorylation. *Cancer Research*. 2002; 62:381-385.
10. Luo H, Tang L, Tang M, et al. Phase IIa chemoprevention trial of green tea polyphenols in high-risk individuals of liver cancer: modulation of urinary excretion of green tea polyphenols and 8-hydroxydeoxyguanosine. *Carcinogenesis*. 2006; 27:262-268.
11. Mereles D, Hunstein, W. Epigallocatechin-3-gallate (EGCG) for Clinical Trials: More Pitfalls than Promises? *Int. J. Mol. Sci*. 2011, 12, 5592-5603.
12. Lu, H.; Meng, X.; Yang, C.S. Enzymology of methylation of tea catechins and inhibition of catechol-O-methyltransferase by (-)-epigallocatechin gallate. *Drug Metab. Dispos*. 2003, 31, 572–579.
13. Ishii, T.; Ichikawa, T.; Minoda, K, et al.. Human serum albumin as an antioxidant in the oxidation of (-)-epigallocatechin gallate: Participation of reversible covalent binding for interaction and stabilization. *Biosci. Biotechnol. Biochem*. 2011, 75, 100–106.
14. Shim, M, Saab S. Severe Hepatotoxicity Due to Hydroxycut: A Case Report. *Digestive Diseases and Sciences*. 2009; 54(2):406-408.

15. Mazzanti G, Menniti-Ippolito F, Moro P, et al. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. *European Journal of Clinical Pharmacology*. 2009; 65(4):331-341.
16. Sarma DN, Barrett ML, Chavez ML, et al. Safety of green tea extracts a systematic review by the US Pharmacopeia. *Drug Safety*. 2008; 31:469–484.
17. [Schrieber J](#), [Wen Z](#), [Vourvahis M](#), et al. The pharmacokinetics of silymarin is altered in patients with hepatitis C virus and nonalcoholic Fatty liver disease and correlates with plasma caspase-3/7 activity. *Drug Metab Dispos*. 2008; 36(9):1909-1916.
18. Schrieber SJ, Hawke RL, Wen Z, et al. Differences in the Disposition of Silymarin Between Patients with Non-Alcoholic Fatty Liver Disease and Chronic Hepatitis C. *Drug Metab Dispos*. 2011; 39(12):2182-2190.
19. Lake AD, Novak P, Fisher CD, et al. Analysis of global and absorption, distribution, metabolism, and elimination gene expression in the progressive stages of human nonalcoholic fatty liver disease. *Drug Metab Dispos*. 2011; 39(10):1954-1960.
20. Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an overview. *Expert Opinion on Drug Safety*. 2007; 6(6):673-684.
21. Foster DR, Sowinski KM, Chow HH, et al. Limited sampling strategies to estimate exposure to the green tea polyphenol, epigallocatechin gallate, in fasting and fed conditions. *Ther Drug Monit*. 2007; 29(6):835-842.
22. El Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med*. 1999; 340:745-750.
23. Calland N, Albecka A, Belouzard S, et al. (-)-Epigallocatechin-3-gallate is a new inhibitor of hepatitis C virus entry. *Hepatology*. 2012; 55(3):720-729.

24. [Ciesek S](#), [von Hahn T](#), [Colpitts CC](#), et al. The green tea polyphenol, epigallocatechin-3-gallate, inhibits hepatitis C virus entry. *Hepatology*. 2011; 54(6):1947-1955.
25. Shimizu M, Shirakami Y, Moriwaki H. Targeting receptor tyrosine kinases for chemoprevention by green tea catechin, EGCG. *Int J Mol Sci*. 2008; 9(6):1034-1049.
26. Seddick M, Lucidarme D, Creusy C, et al. Is Exolise hepatotoxic? *Gastroenterol Clin Biol*. 2001; 25:834-835.
27. Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement Hydroxycut. *Ann Intern Med*. 2005; 142(6):477-478.
28. [Lambert JD](#), [Kennett MJ](#), [Sang S](#), et al. Hepatotoxicity of high oral dose (-)-epigallocatechin-3-gallate in mice. *Food Chem Toxicol*. 2010; 48(1):409-16.
29. Frank J, George TW, Lodge JK, et al. Daily consumption of an aqueous green tea extract supplement does not impair liver function or alter cardiovascular disease risk biomarkers in healthy men. *J Nutr*. 2009; 139(1):58-62.
30. [Chow HH](#), [Cai Y](#), [Hakim IA](#), et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res*. 2003; 9(9):3312-3319.
31. Basu A, Sanchez K, Leyva MJ, et al. Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. *J Am Coll Nutr*. 2010; 29(1):31-40.

32. Brown AL, Lane J, Holyoak C, et al. Health effects of green tea catechins in overweight and obese men: a randomised controlled cross-over trial. *Br J Nutr.* 2011; 106(12):1880-1889.
33. [Ullmann U](#), [Haller J](#), [Decourt JP](#), et al. A single ascending dose study of epigallocatechin gallate in healthy volunteers. *J Int Med Res.* 2003; 31(2):88-101.
34. Chow HH, Cai Y, Alberts DS, et al. Phase I Pharmacokinetic Study of Tea Polyphenols following Single-dose Administration of Epigallocatechin Gallate and Polyphenon E. *Cancer Epidemiology, Biomarkers & Prevention.* 2001; 10:53-58.

Figure 1: EGCG concentrations over time (dosing day).

EGCG concentration over time in cirrhotics and non-cirrhotic controls (open circles and squares, respectively), along with geometric means and 95% confidence intervals for each group (closed circles and squares).