Published in final edited form as:

Food Chem Toxicol. 2015 September ; 83: 26–35. doi:10.1016/j.fct.2015.05.019.

The safety of green tea extract supplementation in postmenopausal women at risk for breast cancer: results of the Minnesota Green Tea Trial

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This trial was registered at clinicaltrials.gov as NCT00917735 on June 8, 2009.

Disclosure of Potential Conflicts of Interest: No potential conflicts of interest are disclosed.

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1. Introduction

Green tea is one of the world's most popular beverages and has been associated with a number of health benefits, including prevention of obesity (Huang et al. 2014), cardiovascular disease (Hodgson and Croft 2010), neurodegenerative diseases (Andrade and Assuncao 2012), and several site-specific cancers, including breast cancer (Yuan 2013). These beneficial effects are primarily attributed to the chemical properties of tea catechins, of which (-)-epigallocatechin-3-gallate (EGCG) is the most abundant (50-75% of total catechin content) and biologically active form (Kao, Hiipakka, Liao 2000). Other important components include epigallocatechin (EGC), epicatechin-3-gallate (ECG), epicatechin (EC), flavonols, and phenolic acids (Yang et al. 2011).

Tea is produced from the leaves of the *Camellia sinensis* plant and is classified into green, black, and oolong varieties based on the distinct processing techniques used for each type. To produce green tea, fresh tea leaves are steamed or heated immediately after harvest to minimize oxidation reactions, which results in maintenance of a high content of catechins, the main polyphenolic constituents in green tea. In contrast, black tea is produced by crushing and fermenting tea leaves after harvest to enhance oxidation and conversion of catechins primarily to theaflavins and thearubigens, which are responsible for the color and flavor characteristics of black tea. Worldwide, green tea accounts for approximately 20% of total tea production (Sang et al. 2011).

Several studies and case reports have described adverse events (AEs) associated with high-dose GTE preparations. Hepatotoxicity, gastrointestinal (GI) complaints (abdominal bloating, dyspepsia, flatulence, nausea, and vomiting), and central nervous system symptoms (agitation, dizziness, headache, and insomnia) are the most commonly reported AEs (Mazzanti et al. 2009; Patel et al. 2013; Sarma et al. 2008). In light of this information, the United States Pharmacopeia (USP) conducted a safety review in 2008 and found 216 AE case reports following the use of multiple GTE preparations, including 34 reports of liver damage. Doses ranged from 0.7 to 3 g catechins per day, and most individuals recovered after termination of use. However, whether or not the hepatotoxicity was due specifically to the GTE was unclear in most cases due to differences in methods of GTE extraction, concomitant medication use, or the presence of additional herbal compounds in the product.

The USP concluded that significant safety issues are minimal if GTEs are formulated correctly and used as directed, and suggested, but did not require, a warning to be placed on any green tea extract marketed as a dietary supplement (Sarma et al. 2008).

Catechins are primarily metabolized through methylation, glucuronidation, sulfation, and ring fission metabolism (Lambert, Sang, Yang 2007). Polymorphisms in catechol-*O*-methyltransferase (COMT), an enzyme involved in the methylation pathway, have been correlated with breast cancer risk. A G to A transition at codon 158 of *COMT* (SNP rs4680) causes a valine to methionine substitution in the cytosolic or membrane-bound form of the enzyme, resulting in a 3- to 4-fold decrease in enzymatic activity (Dawling et al. 2001). Wu, *et al.*, have shown that the breast cancer protective effect of green tea intake is more prominent in women with the homozygous low-activity (A/A) COMT genotype than those with the homozygous high-activity (G/G) genotype (Wu et al. 2003), suggesting that individuals with the low-activity COMT genotype metabolize tea catechins at a slower rate and retain these bioactive components longer in their bodies. This may contribute to prolonged exposure to beneficial compounds within green tea. At the same time, little is known about the effect of variation in COMT enzymatic activity with respect to adverse effects of green tea or GTE consumption.

Given the widespread use of green tea supplements and data suggesting benefits with respect to disease prevention, it is extremely important to clarify the AEs that can be attributed to GTE and if AE incidence is modified by variation in COMT genotype. To accomplish this, we carefully monitored AEs in a randomized, double-blind, placebo-controlled intervention study designed to evaluate the effects of oral decaffeinated GTE supplementation on biomarkers of breast cancer risk. This paper reports in detail the adverse events that occurred in the entire group of 1075 randomized participants.

2. Material and Methods

2.1 Study Design

A detailed description of the Minnesota Green Tea Trial (MGTT) design, eligibility criteria, study conduct, and patient flow through the trial will be published separately (Samavat, et al., pending publication). Briefly, postmenopausal women aged 50 to 70 years and classified as having high mammographic density (>50% fibroglandular tissue) were recruited on the basis of their annual screening mammogram from 2009 to 2013 at 8 clinical centers in the Minneapolis-St. Paul metropolitan area. Of 1075 randomized women, 538 were assigned to receive four oral GTE capsules containing 1315 mg ± 116 total catechins per day (843 ± 44 mg as EGCG) and 537 were randomized to receive placebo for 12 months. Figure 1 depicts the full randomization scheme. Total catechin and EGCG dosage was approximately equivalent to four 8-ounce (240 mL) cups of brewed green tea per day (Bhagwat S, Haytowitz DB, Holden JM 2014). Nine hundred thirty-seven women (87.2%) completed the study. Participants were required to limit brewed green tea consumption to < 1 cup/week and were instructed to take two study capsules with food, twice daily.

Participants, investigators, laboratory staff, and those monitoring clinical outcomes and adverse events were blinded to treatment assignment. The primary objectives were to

determine the effects of GTE supplementation on mammographic density, circulating reproductive hormones and circulating insulin-like growth factor axis proteins. Secondary endpoints included circulating F2-isoprostanes (an established biomarker of oxidative stress), urinary estrogen metabolites, anthropometric variables, and obesity-associated hormone concentrations. Institutional Review Board (IRB) approval was obtained at each clinical center and all participants provided written informed consent.

Women with any of the following characteristics at baseline were ineligible for the present study: (1) tested positive for serological status of hepatitis B surface antigen; (2) tested positive for serological status of antibodies to hepatitis C virus; (3) baseline alanine aminotransferase (ALT) higher than 1.5 times the upper limit of normal (ULN) (defined in this study as 60 U/L); (4) any history of cancer; (5) any history of proliferative breast disease; (6) history of breast augmentation; (7) body mass index (BMI) below 18.5 or above 40 kg/m^2; weight change more than 4.6 kg during the previous 12 months; (8) current or recent (within 6 months) use of hormone replacement therapy; (9) current use of anti-inflammatory agents including methotrexate or Enbrel (etanercept); (10) current smoker; (11) regular consumption of 7 or more alcoholic beverages per week; and (12) regular consumption of 1 or more cups of green tea per week.

2.2. Study Supplement

Green Tea Extract Catechin Complex (Corban complex GTB, referred to as GTE in this publication) and placebo capsules were supplied by Corban Laboratories (Eniva Nutraceutics, Plymouth, MN). Catechin analysis was performed on each batch in the laboratory of CS Yang at Rutgers University. Mean total catechin content of each GTE capsule was 328 ± 30 mg, including 211 ± 11 mg EGCG, 27 ± 30 mg EGC, 51 ± 19 mg ECG, and 27 ± 6 mg EC. Placebo capsules were identical in appearance to GTE and contained 50% (816 mg) maltodextrin, 49.5% (808 mg) cellulose, and 0.5% (8 mg) magnesium stearate. Each capsule contained less than 4 mg caffeine. Participants were instructed to consume two capsules, twice daily with morning and evening meals.

2.3. COMT Genotyping

COMT genotyping was performed by the University of Minnesota Genomics Center. DNA was extracted from buffy coat samples by the Qiagen DNAeasy Blood and Tissue Kit method (Qiagen Inc., Gaithersburg, MD, USA). A TaqMan assay was developed for determining the COMT G/A polymorphism using a TaqMan PCR Core Reagent kit (Applied Biosystems, Foster City, CA). Corriell cell lines with known COMT genotype were used as quality control with each PCR run. Participant genotypes were categorized as follows: homozygous high-activity = G/G (n [GTE] =144; n [Placebo] = 141); homozygous low-activity = A/A (n [GTE] =178; n [Placebo] = 163); heterozygous intermediate-activity = G/A (n [GTE] =216; n [Placebo] = 233).

2.4. Ascertainment of Adverse Events

An AE was defined as any unfavorable or unintended sign, symptom, disease, or abnormal lab value potentially caused by study treatment. Information on AEs occurring during the study period was obtained by specific questioning at clinic visits or by self-report via

telephone or e-mail and was recorded in a source document (see supplemental materials, Figure 1S). AE information was coded and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 (National Cancer Institute May 29, 2009). Events were graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death (Grade 5), with detailed parameters according to the relevant organ system. An AE was considered serious if it was fatal or life threatening, caused persistent or significant disability, or required hospitalization or prolonged hospitalization. Any serious adverse events (SAEs) were coded as Grade 3 or higher by CTCAE v.4.03 guidelines.

Attribution was assessed and recorded by MGTT medical personnel. All reports of AEs were recorded whether or not they were deemed by the investigator to be related to treatment. Actions taken with respect to study supplement and outcome of event were also recorded in the source document. Any clinically significant abnormality or chronic condition noted at the initial screening visit was documented as a pre-existing condition and was only recorded as an AE if the severity of symptoms changed from baseline. All cancer diagnoses, excluding basal or squamous cell carcinoma, were recorded as SAEs.

The clinical course of each event was tracked in an ongoing AE record in the study clinic and each event was followed until resolution. Events occurring more than once in the same participant were recorded as separate events. If a participant experienced an SAE, wished to discontinue taking the study product, and/or was directed to do so by her health care provider, she was taken off product and continued in the study in accordance with the intention to treat (ITT) data analysis model. These participants completed all study requirements as directed in the consent form – including attendance at clinic visits, collection of blood and urine samples, and completion of questionnaires - with the exception of consumption of study product.

Participants with an ongoing AE at their final clinic visit continued to be followed for 30 days after the last administration of study treatment. SAEs that were ongoing at the end of the study period were followed up until determination of the final outcome or unless the participant refused to be further contacted. Participants experiencing a diagnosis requiring ongoing medical or surgical treatment were asked to provide formal documentation of their diagnosis. With the exception of one request for the code to be broken due to a Grade 4 SAE, study investigators were kept blinded to the assigned treatment of all participants experiencing an AE.

2.5. Data Safety and Monitoring Board

Preplanned interim analyses of adverse events were conducted biannually in 2011 and 2012 and annually in 2013 and 2014. Information was presented to an independent data and safety monitoring board (DSMB) responsible for reviewing side effect and toxicity data, proposing corrective actions for unexpectedly severe side effects, and reviewing the impact of other scientific investigations that may affect the conduct of the MGTT trial.

2.6. Stopping Rules for Study Product Use

Since GTE supplementation has previously been associated with hepatotoxicity (Mazzanti et al. 2009; Patel et al. 2013; Sarma et al. 2008), specific policies were established to monitor liver enzyme concentrations and stopping rules were approved by study-affiliated medical personnel and the DSMB. Under the advisement of study physicians, ALT elevations formed the basis of corrective action taken for study participants due to its sensitivity and specificity in diagnosing hepatocellular damage (Pratt and Kaplan 2000).

Hepatic function was measured monthly during the first six months of the study and at months 9 and 12 (Quest Diagnostics, Wood Dale, IL). . At the start of the clinical trial, participants' ALT concentrations were evaluated at the screening visit and monthly from months 1-12, in order to monitor possible hepatotoxicity. In the trial's third year, clinic visits at months 7, 8, 10, and 11 were eliminated with Food and Drug Administration (FDA) and IRB approval due to low incidence of ALT elevations (0.66% of all tests performed) and rarity of occurrence after month 6. Participants with an ALT elevation prior to month 6 or whose transaminase levels were near a Grade 1 elevation at month 6 had the option to receive monthly hepatic panels for the duration of the study.

Hepatic panel results were available within 2 business days of analysis. A participant found to have ALT concentrations considered a Grade 1 (1.5-3.0 times the upper limit of normal [ULN], ULN = 60 U/L) or Grade 2 (>3.0-5.0 times ULN) elevation was asked to refrain from taking study product for 14 days, at which time a hepatic panel re-test was completed. If the values from the re-test were within acceptable range (below 1.5 times ULN), the participant was put back on product. If values remained elevated, the participant was asked to complete another re-test after 14 days. The participant was tested every two weeks until ALT concentrations returned to below 1.5 times ULN, at which time she was asked to resume taking product. An ALT elevation classified as Grade 3 (>5.0 times ULN) or 4 (>20.0 times ULN) was considered an SAE. In the event of a Grade 3 or 4 ALT elevation, participants were permanently taken off study product but asked to continue in the study. Participants were re-tested at 14-day intervals until their ALT concentration returned to within normal range. The principle investigator, National Institutes of Health (NIH), FDA, study IRB, product manufacturer and study DSMB were contacted within their required notification periods when these events occurred.

Specific stopping rules were not established for other AEs and participants continued to consume study product during ongoing AEs not documented as an ALT elevation. All AEs were followed until resolution or until 30 days after conclusion of participation.

2.7. Statistical Analysis

All randomized participants (n = 1075) were included in the statistical analysis. AEs were numerically coded based on body system and specific symptom using the NCI CTCAE, version 4.03 (National Cancer Institute May 29, 2009). All statistical analyses were conducted using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). To examine the difference in baseline characteristics and AEs by treatment group and AE status, the Chi-square test or Fisher's exact test was used for categorical variables and Student's *t*-test was used for

continuous variables. Continuous variables are reported as means and standard deviations and categorical variables are reported as counts and percentages. For participants who reported multiple AEs within a given category (system or symptom), the most severe AE per category is presented. All reported *P*-values are two-sided; statistical significance was set at $P < 0.05$. Differences between groups for frequencies of several types of AEs were examined in statistical analysis but adjustments for multiple endpoints, such as the Bonferroni method, were not used, as is common in AE assessment.

3. Results

3.1. Participant Disposition

Out of 1075 participants, 39 randomized to GTE and 20 randomized to placebo stopped taking study product but remained in the study, in accordance with the ITT statistical model. Participants mainly stopped taking product due to adverse symptoms (n = 50); the remainder became ITT due to personal request (n = 6) or protocol deviations (n = 3). An additional 138 withdrew from participation. Reasons for withdrawal included participant request (n = 93), adverse event (n = 22), protocol violation (n = 10), lost to follow-up (n = 10), investigator judgment (n = 3), and death (n = 1). Of the participants who withdrew due to AEs, 18 of 22 (82%) were randomized to GTE.

3.2. Baseline Characteristics

Baseline demographics and participant information are presented in Table 1. On average, women were 60 years old, 10.8 years postmenopausal, primarily white (97.8%), and had a mean BMI of 25.6 kg/m^2. Regular tea consumption was reported by 60.6% (564 of 931 recorded responses) and 24.5% had at least one first-degree relative with breast cancer (253 of 1031 responses). No statistically significant differences in these characteristics were observed between participants randomized to GTE compared to those randomized to placebo Total energy intake and intake of macro- and micronutrients did not differ between GTE and placebo groups (data not shown for all dietary variables). No differences in body weight, BMI, or waist-hip circumference were noted between groups. No statistically significant differences in baseline characteristics were observed when comparing those with and without AEs between and within groups, except that participants randomized to GTE with at least one AE were shorter, had obtained a lower level of education, and were younger at the time of their first live birth as compared to participants randomized to placebo with at least one AE.

3.3 Adverse Events

Adverse events listed by CTCAE category and severity are shown in Table 2. In total, there were 1141 AEs documented in participants randomized to GTE; 1031 were recorded in the placebo group. Overall, no statistically significant differences were seen in AE incidence in the 6 categories contributing to the majority of reported events. Infections (e.g. upper respiratory infection, sinusitis, cough, sore throat) were the most commonly experienced AEs (216 vs. 217 events in GTE and placebo, respectively, in 139 (25.8%) vs. 145 (27.0%) participants, $P = 0.67$), followed by GI disorders (235 vs. 184 events in GTE and placebo, in 137 (25.5%) vs. 123 (22.9%) participants, $P = 0.33$). When comparing all CTCAE system

categories (Table 3), 18 GTE participants experienced an AE in the "Skin and Subcutaneous Tissue Disorders" category as compared to 8 in the placebo group ($P = 0.05$). Of those assigned to GTE, 9 participants experienced symptoms coded as a rash or allergic skin reaction (either Grade 1 or 2) as compared to 1 in the placebo group (data not shown). A greater percentage of GTE participants experienced AEs coded as "Investigations" compared to placebo (8.2% vs. 2.6%, $P < 0.001$); this was primarily due to the inclusion of ALT elevations in this system category.

Groups did not statistically differ in severity of AEs. Hypertension and upper respiratory infection/cough were the main non-GI events that contributed appreciable numbers to total AEs (Table 1S). Eleven participants randomized to GTE experienced 13 Grade 3 SAEs as compared to 7 participants experiencing 8 Grade 3 SAEs in those randomized to placebo ($P = 0.34$) (Table 2). One ALT elevation coded as Grade 4 occurred in the GTE group and one death (Grade 5) was recorded for a participant in the placebo group, who was killed in a motor vehicle accident. No statistically significant differences by COMT genotype were observed in any AE category (Table 2S).

3.3.1. Gastrointestinal Events—Detailed information on GI AEs is presented in Table 4. The number of participants reporting nausea was greater in the GTE group as compared to placebo (55 (10.2%) vs. 26 (4.8%), $P < 0.001$). Forty-three participants (8.0%) receiving placebo reported at least one instance of diarrhea as compared to 24 (4.5%) in the GTE group; this was statistically significant ($P < 0.02$). Groups did not statistically differ in number of participants reporting any other GI AE and no differences were observed in GI AE severity.

3.3.2. ALT Elevations—Statistically significant differences between GTE and placebo groups were observed in ALT elevations, as detailed in Table 5. Forty participants (3.7% of all participants) experienced a total of 57 ALT elevations. Of these, 36 participants were randomized to GTE and 4 to placebo ($P < 0.001$). Thirty-nine of 53 elevations in the GTE group (74.4%) and 4 of 4 in the placebo group (100%) were classified as a Grade 1 elevation. Seven Grade 2 ALT elevations, 6 Grade 3 elevations, and one Grade 4 elevation were documented in participants receiving GTE. Average length to resolution for all ALT elevations was 30.2 days (data not shown). With the exception of one case, the elevation subsided when GTE consumption was discontinued (dechallenge). A positive rechallenge occurred in 12 cases. Three participants randomized to GTE experienced 3 or more ALT elevations during the intervention period (all Grades 1 or 2). All elevations in the placebo group were single occurrences with no repeated elevations. Incidence of ALT elevation did not differ by COMT genotype (Table 2S).

3.3.3. Serious Adverse Events—Detailed information on all SAEs is presented in Table 3S. Fourteen SAEs (CTCAE Grades 3-5) were documented in 12 participants in the GTE group as compared to 9 SAEs in 8 participants randomized to placebo ($P = 0.30$). Nine of the 14 in GTE group were ALT or aspartate aminotransferase (AST) elevations; other categories included surgical and medical procedures (n = 3), neoplasms (n = 1), and GI disorders (n = 1). In the placebo group, 2 SAEs were documented in each of the following: surgical and medical procedures; neoplasms; and injury, poisoning, and procedural

complications. One SAE was recorded in each of the following: vascular disorders, GI disorders, and metabolism and nutrition disorders. All surgeries in both GTE and placebo groups were the result of elective procedures and/or pre-existing conditions.

3.3.4. Cancer Incidence—Two participants (0.2%) assigned to placebo were diagnosed with uterine cancer after randomization; one received her diagnosis one day after beginning study product and the other was diagnosed during the last month of participation (Table 3S). Two women (one participant randomized to GTE, one to placebo) reported a diagnosis of non-melanoma skin cancer during the study.

4. Discussion

Green tea has been associated with health benefits for centuries, and many green tea supplements are now commercially available. This trial was designed to test the effects of a green tea extract supplement on markers of breast carcinogenesis. Given that AEs have been associated with green tea supplement consumption in the past, it is extremely important to determine the incidence of AEs in order to evaluate the benefit in relation to the risk. Thus, the MGTT sought to determine the effect of GTE containing 1315 ± 116 mg total catechins/day (843 ± 44 mg as EGCG) on breast cancer risk factors in postmenopausal women at high risk for breast cancer. This paper reports on the adverse effects observed in MGTT participants.

Twenty-six serious adverse events (CTCAE Grade 3-5) occurred in 20 participants (Table 3S). Twelve of these participants were randomized to GTE, and 7 of 12 (58%) experienced SAEs related to ALT elevations. The 5 remaining GTE participants with an SAE had either reported a pre-existing condition related to the SAE at baseline, had experienced symptoms prior to randomization, or had been off study product for more than 4 months at the time of the SAE. Therefore, aside from ALT elevations, it is unlikely that GTE was the principal contributing factor to the participant's condition. In the current study, 7 ALT elevations were classified as SAEs, which highlights the serious hepatotoxicity risk that individuals should consider when initiating high-dose GTE consumption. However, a singular attribution to GTE could not be determined in any of these cases, as all were associated with simultaneous infection, use of new medication, alcohol consumption, or self-reported past medical history of liver enzyme elevations.

Overall, AE incidence did not differ in any of the six system categories that contributed the majority of all AEs, which included infections; vascular disorders; respiratory, thoracic and mediastinal disorders; general disorders; musculoskeletal and connective tissue disorders; and GI disorders (Table 2). Statistically significant between-group differences were seen in two GI-related AEs - nausea and diarrhea. GTE consumption was associated with increased nausea as compared to placebo. GI distress is a noted adverse effect of high-dose green tea consumption (Yang et al. 1998) and is especially evident when GTE is administered in the fasted state, presumably in relation to the increased bioavailability of active polyphenolic components (Chow et al. 2005). Many of the nausea-related AEs resolved after clinic staff emphasized the recommendation to take study product with a meal, which supports other studies that have demonstrated that green tea preparations containing 800 mg EGCG are

generally well-tolerated (Chow et al. 2003; Ullmann et al. 2004). Additionally, only one GI-related SAE (Grade 3) occurred in the group receiving GTE (Table 1S), indicating that a minimal number of severe GI responses were seen in the current trial.

Incidence of diarrhea was nearly twice as high in participants assigned to placebo as compared to those in the GTE group. Placebo capsules were mainly composed of maltodextrin and cellulose. Maltodextrin has been shown to induce osmotic diarrhea at quantities exceeding 1 g/kg body weight daily (Kishimoto et al. 2013; Livesey 2001). Placebo capsules contained a total of 816 mg maltodextrin/day (0.01 g/kg/day, based on average weight of 67.8 kg in placebo group); therefore, although we cannot exclude the possibility that maltodextrin contributed to the increased incidence of diarrhea among participants, we think it is unlikely, given the dose. Cellulose is broadly used in the manufacture of pill tablets, and though it has been established that it is beneficial for alleviating constipation (Gallaher DD 2001; Yang et al. 2012), it has not been cited as a possible contributor to diarrheal symptoms. In fact, concomitant administration of cellulose with maltodextrin has been suggested to suppress osmotic diarrhea (Oku, Hongo, Nakamura 2008), though this effect has not been confirmed. It is unclear why more participants assigned to placebo experienced this AE; however, factors such as concomitant illness, use of new medication, and other factors not disclosed by participants may have contributed to the difference. It is also possible that GTE may be protective against diarrheal symptoms. One recent randomized trial (Emami et al. 2014) determined that administration of green tea reduced the frequency and severity of diarrhea in patients undergoing pelvic radiotherapy. Additional research is needed to confirm this effect.

There were statistically significant differences between groups in two CTCAE categories: Skin and Subcutaneous Tissue Disorders and Investigations, which included ALT elevations (Table 3). More participants randomized to GTE experienced skin-related AEs as compared to placebo; most predominant of these were rash and allergic skin reaction. Two other randomized trials (Nantz et al. 2009; Widlansky et al. 2007) have reported incidence of rash with administration of GTE at much lower doses than was given in our study (300 mg EGCG and 200 mg GTE with >45% as EGCG, respectively), though investigators did not determine if the symptom occurred as a direct result of GTE consumption. These AEs were generally mild and occurred in a small percentage of the total study population. To our knowledge, no randomized trial has investigated the relationship of green tea or its concentrated extracts with adverse dermatologic responses. While green tea is not a common allergen, it is possible the study product caused an adverse immune response in this subset of our study population. Based on these events and those occurring in other studies, additional research is needed to determine mechanisms linking GTE consumption to skin irritation and antigen-mediated allergic reaction.

More participants taking GTE experienced at least one ALT elevation than in participants randomized to placebo (36 [6.7%] vs. 4 [0.7%], $P < 0.001$; Table 5). Our findings support those of previous studies that have shown a relationship between high-dose GTE consumption and liver transaminase elevations. Though green tea has typically been associated with antioxidant effects, recent research has demonstrated a strong pro-oxidant effect of green tea catechins (especially EGCG) that can cause hepatotoxicity when

administered at high doses (Galati et al. 2006; Lambert and Elias 2010; Mazzanti et al. 2009). Mechanisms for GTE-induced liver injury include mitochondrial membrane destruction and induction of reactive oxygen species (Galati et al. 2006; Kim, Quon, Kim 2014). These processes lead to hepatocyte damage and release of cell contents including ALT, a sensitive and specific marker of hepatic inflammation. Galati, *et al*., (Galati et al. 2006) found that EGCG was the most cytotoxic tea phenolic to rat hepatocytes and mice *in vivo*, though to our knowledge no study has examined this effect in humans. Hepatotoxic reactions tended to show a temporal relationship between GTE consumption and effect onset: 26 of 36 participants (72%) had been taking GTE for 4 months or less, which is consistent with previous reports GTE-induced toxicity mainly manifesting after roughly 3 months of consumption (Mazzanti et al. 2009). Furthermore, a rechallenge with GTE resulted in another ALT elevation in 12 participants, suggestive of a causal association between GTE intake and hepatotoxicity in these participants.

Several case reports have implicated GTE supplements as a cause of hepatotoxicity; yet, this association has not been consistently observed in controlled intervention studies. While this may be due in part to short intervention periods, lower doses of GTE, differences in GTE composition, and lifestyle factors of study participants, the rarity and heterogeneity of these observations suggests that genetic variability may have considerable influence on predisposition for GTE-induced hepatoxicity. In an analysis of 16 case reports of GTE-induced liver injury, Navarro, *et al.*, reported no correlation between daily or total catechin dose and peak liver enzyme values, disease severity, or causality (Navarro et al. 2013). In our study, ALT elevations were only seen in a small percentage of participants (6.7% of those randomized to GTE compared with 0.7% in placebo; 1.3% of GTE consumers compared with no participants in placebo experienced ALT-related SAEs). This observation points to the role that inter-individual differences play in hepatotoxicity risk. No difference in incidence of ALT elevation was observed between COMT genotypes in our study. However, our genotypic analysis was limited to one specific polymorphism of one enzyme involved in catechin metabolism, and it is clear that continued research is needed to define genetic host factors that may influence relative toxicity risk. Recent studies have begun to use unique translational and genomics approaches to determine the association between GTE dosage, hepatic abnormalities, and specific gene variants that may eventually identify sub-populations at risk for GTE toxicity (Church et al. 2014; James, Forester, Lambert 2014).

There were a number of strengths of the MGTT. Its large sample size made it possible to detect statistical differences even for relatively uncommon conditions. The 12-month study duration allowed for the determination of relatively long-term effects of GTE supplementation, which improves upon previous studies with a typical maximum intervention period of 3 months. The MGTT employed the NCI's CTCAE v.4.03 (National Cancer Institute May 29, 2009), an NIH-supported disease classification system, which provided a standardized and consistent method for AE assessment across a wide variety of clinical signs and symptoms.

Yet, our trial is not without limitations. The generalizability of our findings is limited to postmenopausal, primarily Caucasian women with high mammographic density not

currently receiving systemic menopausal hormone therapy. However, since this population is significantly affected by breast cancer diagnoses, we believe that women in this group may be particularly interested in alternative or adjuvant preventive measures such as green tea extract supplementation. Only one standard dose of green tea catechins was administered - on average, 843 ± 44 mg EGCG per day, which is equivalent to approximately four 8-ounce (240 mL) cups of a prepared green tea infusion (Bhagwat S, Haytowitz DB, Holden JM 2014). While this amount is higher than that typically consumed in Western populations, it is within the range of green tea consumption in some Asian countries, which formed the basis of our dosing scheme. Though it may be possible to achieve similar catechin administration through oral consumption or topical green tea preparations, the results of this study pertain specifically to green tea catechins administered as capsules containing a concentrated extract. Results may not be extrapolated to alternative dosing methods until further bioavailability research is conducted.

Elevations in liver transaminases may occur for a wide variety of reasons unrelated to GTE consumption, including medication use, alcohol abuse, and liver disease (Pratt and Kaplan 2000). This presented a challenge in definitively determining causality of ALT elevations, though efforts were made to gather pertinent health information from participants at each clinic visit. Through pre-screening for elevated ALT and hepatitis B and C antigens prior to randomization, potential participants with conditions associated with chronically elevated ALT (e.g. hepatitis, steatosis, nonalcoholic steatohepatitis, inherited diseases such as hemochromatosis and Wilson's Disease) did not meet eligibility criteria and were not included in this study sample. Other causes of elevated ALT cannot be ruled out in study participants, and some women did report use of new medication(s), increased alcohol consumption, or recent illness at the time of their hepatic function test. However, randomization likely balanced the impact that such factors would have on liver enzyme status.

5. Conclusion

Results of the present study suggest that daily intake of 1315 mg of green tea catechins containing 843 mg EGCG posed mainly mild, transient adverse effects in a small percentage of the study population and is safe for most Caucasian postmenopausal women. Liver enzyme abnormalities were confirmed as the primary concerning factor related to GTE consumption. Our results correspond with the USP's review of the use of GTE, which concluded that (1) significant safety issues are minimal if GTEs are formulated correctly and used as directed; (2) doses associated with significant adverse effects ranged from 0.7 to 3 g catechins per day; and (3) most cases resolved after termination of product consumption (Sarma et al. 2008). Given its low toxicity risk and long-term widespread consumption, green tea and concentrated catechin extracts have potential for use as a safe, natural supplement for breast cancer risk reduction in healthy populations. Doses of GTE high enough to cause adverse events, including hepatotoxicity, are not well established and may be dependent on many factors, including genetic variation, nutritional status, and bioavailability of green tea catechins. Additional dose-response studies employing detailed, systematic attribution systems are needed to determine an optimal effective dose for maximum clinical benefits and minimum adverse effects, specific characteristics of

populations at increased risk for GTE-related adverse effects, and targeted applications for GTE supplementation to reduce disease risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors acknowledge the support of the NIH and National Cancer Institute. The authors thank the study radiologists: Drs. Tim Emory, Jessica Kuehn-Hajder, and Megan Mckeon; University of Minnesota Medical Center and Park Nicollet co-investigators: D. Yee, K. Swenson; clinical monitor: K. Mischke; clinical staff: A. Brehm, J. Mobeck-Wilson, S. Kjellberg Muehlhausen, K. Ringsak; laboratory staff: L. Carpenter, W.E. Smith, M. Wachter; and research support staff: A. Egan, J. Nissen, and A. Schumacher, for their contributions to our research.

Financial Support: Research reported in this publication was supported by the National Institutes of Health/ National Cancer Institute grant R01 CA127236, Award Number T32CA132670 from the National Cancer Institute, the Department of Defense/U.S. Army Medical Research and Materiel Command Award Number W81XWH-11-1-0013, the University of Minnesota Agricultural Experiment Station Project Number MIN-18-103, and the National Center for Advancing Translational Sciences of the National Institutes of Health Award Number UL1TR000114. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. The funding sources and study supplement provider did not contribute to the design or conduct of the study, nor to the writing or submission of this manuscript.

References

Andrade JP, Assuncao M. Protective effects of chronic green tea consumption on age-related neurodegeneration. Curr Pharm Des. 2012; 18(1):4–14. [PubMed: 22211685]

Bhagwat, S.; Haytowitz, DB.; Holden, JM. USDA database for the flavonoid content of selected foods. . Report nr 3. 2014.

Chow HH, Cai Y, Hakim IA, Crowell JA, Shahi F, Brooks CA, Dorr RT, Hara Y, Alberts DS. 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): 3312–9. [PubMed: 12960117]

Chow HH, Hakim IA, Vining DR, Crowell JA, Ranger-Moore J, Chew WM, Celaya CA, Rodney SR, Hara Y, Alberts DS. Effects of dosing condition on the oral bioavailability of green tea catechins after single-dose administration of polyphenon E in healthy individuals. Clin Cancer Res. 2005a; 11(12):4627–33. [PubMed: 15958649]

Church RJ, Gatti DM, Urban TJ, Long N, Yang X, Shi Q, Eaddy JS, Mosedale M, Ballard S, Churchill GA, et al. Sensitivity to hepatotoxicity due to epigallocatechin gallate is affected by genetic background in diversity outbred mice. Food Chem Toxicol. 2014; 76C:19–26. [PubMed: 25446466]

Dawling S, Roodi N, Mernaugh RL, Wang X, Parl FF. Catechol-O-methyltransferase (COMT)-mediated metabolism of catechol estrogens: Comparison of wild-type and variant COMT isoforms. Cancer Res. 2001; 61(18):6716–22. [PubMed: 11559542]

Emami H, Nikoobin F, Roayaei M, Ziya HR. Double-blinded, randomized, placebo-controlled study to evaluate the effectiveness of green tea in preventing acute gastrointestinal complications due to radiotherapy. J Res Med Sci. 2014; 19(5):445–50. [PubMed: 25097628]

Galati G, Lin A, Sultan AM, O'Brien PJ. Cellular and in vivo hepatotoxicity caused by green tea phenolic acids and catechins. Free Radic Biol Med. 2006; 40(4):570–80. [PubMed: 16458187]

Gallaher, DDSB. Dietary fiber. In: Bowman, BARR., editor. Present knowledge in nutrition. ILSI Press; Washington DC: 2001. p. 83

Hodgson JM, Croft KD. Tea flavonoids and cardiovascular health. Mol Aspects Med. 2010; 31(6): 495–502. [PubMed: 20837049]

Huang J, Wang Y, Xie Z, Zhou Y, Zhang Y, Wan X. The anti-obesity effects of green tea in human intervention and basic molecular studies. Eur J Clin Nutr. 2014

James KD, Forester SC, Lambert JD. Dietary pretreatment with green tea polyphenol, (-)-epigallocatechin-3-gallate reduces the bioavailability and hepatotoxicity of subsequent oral bolus doses of (-)-epigallocatechin-3-gallate. Food Chem Toxicol. 2014; 76C:103–8. [PubMed: 25528115]

Kao YH, Hiipakka RA, Liao S. Modulation of endocrine systems and food intake by green tea epigallocatechin gallate. Endocrinology. 2000; 141(3):980–7. [PubMed: 10698173]

Kim HS, Quon MJ, Kim JA. New insights into the mechanisms of polyphenols beyond antioxidant properties; lessons from the green tea polyphenol, epigallocatechin 3-gallate. Redox Biol. 2014; 2:187–95. [PubMed: 24494192]

Kishimoto Y, Kanahori S, Sakano K, Ebihara S. The maximum single dose of resistant maltodextrin that does not cause diarrhea in humans. J Nutr Sci Vitaminol (Tokyo). 2013; 59(4):352–7. [PubMed: 24064737]

Lambert JD, Elias RJ. The antioxidant and pro-oxidant activities of green tea polyphenols: A role in cancer prevention. Arch Biochem Biophys. 2010; 501(1):65–72. [PubMed: 20558130]

Lambert JD, Sang S, Yang CS. Biotransformation of green tea polyphenols and the biological activities of those metabolites. Mol Pharm. 2007; 4(6):819–25. [PubMed: 17963356]

Livesey G. Tolerance of low-digestible carbohydrates: A general view. Br J Nutr. 2001; 85(Suppl 1):S7–16. [PubMed: 11321031]

Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, Mastrangelo S. Hepatotoxicity from green tea: A review of the literature and two unpublished cases. Eur J Clin Pharmacol. 2009; 65(4):331–41. [PubMed: 19198822]

Nantz MP, Rowe CA, Bukowski JF, Percival SS. Standardized capsule of camellia sinensis lowers cardiovascular risk factors in a randomized, double-blind, placebo-controlled study. Nutrition. 2009; 25(2):147–54. [PubMed: 18848434]

National Cancer Institute. Common terminology criteria for adverse events v4.0. May 29. 2009 NCI, NIH, DHHS NIH publication # 09-7473

Navarro VJ, Bonkovsky HL, Hwang SI, Vega M, Barnhart H, Serrano J. Catechins in dietary supplements and hepatotoxicity. Dig Dis Sci. 2013; 58(9):2682–90. [PubMed: 23625293]

Oku T, Hongo R, Nakamura S. Suppressive effect of cellulose on osmotic diarrhea caused by maltitol in healthy female subjects. J Nutr Sci Vitaminol (Tokyo). 2008; 54(4):309–14. [PubMed: 18797153]

Patel SS, Beer S, Kearney DL, Phillips G, Carter BA. Green tea extract: A potential cause of acute liver failure. World J Gastroenterol. 2013; 19(31):5174–7. [PubMed: 23964154]

Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med. 2000; 342(17):1266–71. [PubMed: 10781624]

Sang S, Lambert JD, Ho CT, Yang CS. The chemistry and biotransformation of tea constituents. Pharmacol Res. 2011; 64(2):87–99. [PubMed: 21371557]

Sarma DN, Barrett ML, Chavez ML, Gardiner P, Ko R, Mahady GB, Marles RJ, Pellicore LS, Giancaspro GI, Low Dog T. Safety of green tea extracts : A systematic review by the US pharmacopeia. Drug Saf. 2008; 31(6):469–84. [PubMed: 18484782]

Ullmann U, Haller J, Decourt JD, Girault J, Spitzer V, Weber P. Plasma-kinetic characteristics of purified and isolated green tea catechin epigallocatechin gallate (EGCG) after 10 days repeated dosing in healthy volunteers. Int J Vitam Nutr Res. 2004; 74(4):269–78. [PubMed: 15580809]

Widlansky ME, Hamburg NM, Anter E, Holbrook M, Kahn DF, Elliott JG, Keaney JF Jr, Vita JA. Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease. J Am Coll Nutr. 2007; 26(2):95–102. [PubMed: 17536120]

Wu AH, Tseng CC, Van Den Berg D, Yu MC. Tea intake, COMT genotype, and breast cancer in asian-american women. Cancer Res. 2003; 63(21):7526–9. [PubMed: 14612555]

Yang CS, Wang H, Li GX, Yang Z, Guan F, Jin H. Cancer prevention by tea: Evidence from laboratory studies. Pharmacol Res. 2011; 64(2):113–22. [PubMed: 21397027]

Yang CS, Chen L, Lee MJ, Balentine D, Kuo MC, Schantz SP. Blood and urine levels of tea catechins after ingestion of different amounts of green tea by human volunteers. Cancer Epidemiol Biomarkers Prev. 1998; 7(4):351–4. [PubMed: 9568793]

Yang J, Wang HP, Zhou L, Xu CF. Effect of dietary fiber on constipation: A meta analysis. World J Gastroenterol. 2012; 18(48):7378–83. [PubMed: 23326148]

Yuan JM. Cancer prevention by green tea: Evidence from epidemiologic studies. Am J Clin Nutr. 2013; 98(6 Suppl):1676S–81S. [PubMed: 24172305]

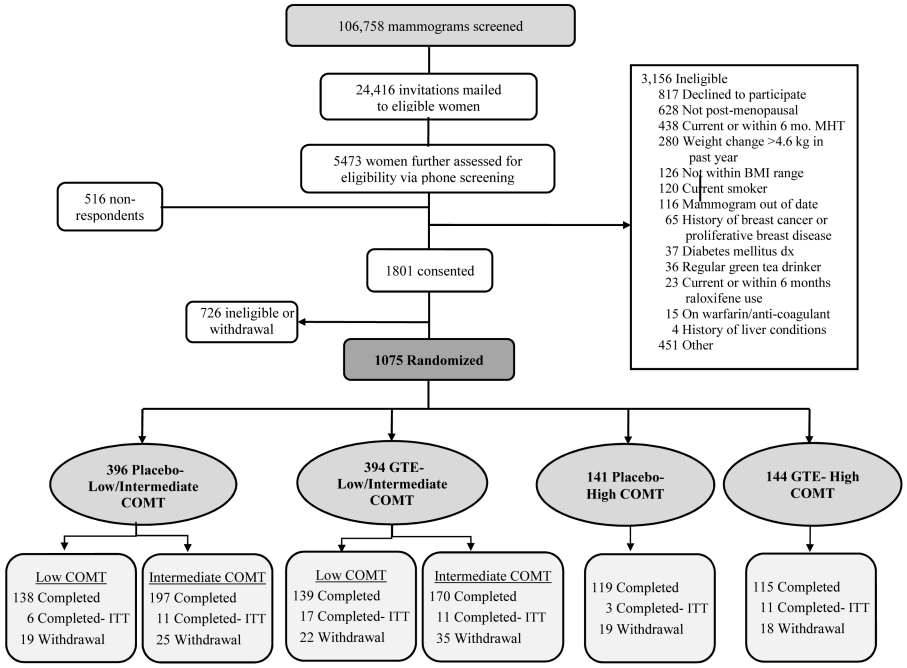

Figure 1.

Flow Diagram of Participant Screening, Enrollment, Randomization, and Follow-up of the Minnesota Green Tea Trial.

Abbreviations: BMI, body mass index; COMT, catechol-*O*-methyltransferase; GTE, green tea extract; ITT, intention-to-treat; MHT, menopausal hormone therapy.

Table 1

Baseline Characteristics of MGTT Participants

	GTE (n=538)	Placebo (n=537)	*P*-value
Age at baseline, y	59.9 (5.0)	59.6 (5.1)	0.35
Body weight, kg	67.4 (10.6)	67.9 (10.5)	0.41
Height, cm	163.1 (9.1)	164.0 (8.7)	0.11
Body mass index, kg/m^2	25.8 (8.7)	25.6 (8.1)	0.81
Waist-hip ratio	0.84 (0.10)	0.83 (0.10)	0.26
Caucasian, n (%)	515 (97.9)	505 (96.9)	0.37
Smoking status, n (%)			0.98
Never	357 (68.1)	356 (68.2)	
Former	167 (31.9)	166 (31.8)	
Alcohol, drinks/week[a]	3.3 (3.0)	3.4 (3.0)	0.77
Physical activity, MET-hr/week	45.3 (53.1)	51.4 (104.0)	0.23
Education, n (%)			0.15
High school or less	33 (6.3)	39 (7.5)	
Some college	112 (21.4)	88 (17.0)	
College degree	236 (45.0)	225 (43.4)	
Postgraduate/professional degree	143 (27.3)	166 (32.1)	
Age at first live birth, y[b]	27.8 (5.4)	28.4 (5.5)	0.16
Years postmenopausal	10.9 (7.8)	10.3 (7.2)	0.20
Family history of breast cancer, n (%)			0.58
No	384 (74.7)	394 (76.2)	
Yes	130 (25.3)	123 (23.8)	
Total energy intake, kcal/d	1438.3 (537.5)	1447.5 (524.7)	0.79
Protein, g/d	58.9 (24.2)	57.6 (22.2)	0.42
% Energy from protein	16.3 (2.8)	16.0 (2.7)	0.06
Fat, g/d	53.3 (25.0)	54.1 (25.3)	0.63
% Energy from fat	32.9 (6.8)	33.14 (6.5)	0.55
Total Carbohydrate, g/d	179.3 (67.9)	181.9 (69.5)	0.55
% Energy from carbohydrate	50.4 (7.5)	50.4 (7.3)	0.95
Dietary fiber, g/d	17.5 (8.2)	17.7 (8.0)	0.72
Tea, servings/week[c]	4.0 (3.8)	4.3 (4.4)	0.44
Caffeine, mg/d	353.6 (312.1)	379.1 (322.7)	0.22

Data presented as means (SD) for continuous variables and as frequencies (%) for categorical variables.

[a] Among alcohol drinkers only. GTE: n=418; Placebo: n=434.:

[b] Among parous women only. GTE: n=407; Placebo: n=393.

[c] Among tea drinkers only. GTE: n=275; Placebo: n=289.:

Abbreviations: GTE, green tea extract; MET-hr, metabolic equivalent hours; MGTT, Minnesota Green Tea Trial.

Table 2

Adverse Events by CTCAE Category[a] and Severity in GTE and Placebo Groups

		Adverse Events (No.)			# Participants (%) with Adverse Events [b]		
		GTE	Placebo	Total	GTE (n=538)	Placebo (n=537)	*P*-value
CTCAE Category	Infections and Infestations	216	217	433	139 (25.8)	145 (27.0)	0.67
	GI Disorders	235	184	419	137 (25.5)	123 (22.9)	0.33
	Vascular Disorders	154	144	298	132 (24.5)	125 (23.3)	0.63
	Respiratory, Thoracic and Mediastinal Disorders	122	122	244	83 (15.4)	85 (15.8)	0.86
	General Disorders and Administration Site Condition	69	77	146	58 (10.8)	60 (11.2)	0.84
	Musculoskeletal and Connective Tissue Disorders	65	69	134	59 (11.0)	55 (10.2)	0.70
	Others[c]	280	218	498	190 (35.3)	165 (30.7)	0.11
Grade (Severity) [d]	1	848	754	1602	359 (66.7)	344 (64.0)	0.36
	2	279	268	547	172 (32.0)	170 (31.7)	0.91
	3	13	8	21	11 (2.0)	7 (1.3)	0.34
	4	1	0	1	1 (0.2)	0 (0)	1.00[e]
	5	0	1	1	0 (0)	1 (0.2)	1.00[e]
Totals		1141	1031	2172			---

[a] Adverse events coded using NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

[b] Data presented as number of participants (% total participants). For participants who reported multiple adverse events within a given system category, the most severe AE per subject, per system is presented.

[c] Includes categories contributing < 5% each to total number of adverse events: surgical and medical procedures; investigations; injury, poisoning and procedural complications; neoplasms (benign, malignant and unspecified (including cysts and polyps)); social circumstances; and disorders of the following systems (in descending order of number of events): nervous; psychiatric; reproductive system and breast; skin and subcutaneous tissue; ear and labyrinth; eye; renal and urinary; cardiac; immune system; metabolism and nutrition; endocrine; blood and lymphatic system; congenital, familial and genetic; and hepatobiliary (not including liver enzyme abnormalities).

[d] Grade: 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=death.

[e] Based on Fisher's exact test.

Abbreviation: GTE, green tea extract.

Table 3

Additional Adverse Events by CTCAE System Category[a]

CTCAE System Category	Total Events (No.)		# Participants (%) with Adverse Events [b]		
	GTE	Placebo	GTE (n = 538)	Placebo (n = 537)	*P*-value
Surgical and Medical Procedures	46	48	39 (7.3)	41 (7.6)	0.81
Investigations	67	14	44 (8.2)	14 (2.6)	<0.001
Nervous	36	34	34 (6.3)	33 (6.2)	0.91
Injury, Poisoning and Procedural Complications	27	29	19 (3.5)	22 (4.1)	0.63
Psychiatric	22	11	17 (3.2)	11 (2.1)	0.25
Reproductive System and Breast	12	19	12 (2.2)	17 (3.2)	0.34
Skin and Subcutaneous Tissue	19	8	18 (3.4)	8 (1.5)	0.05
Ear and Labyrinth	10	10	9 (1.7)	9 (1.7)	1.00
Eye	6	14	6 (1.1)	13 (2.4)	0.10
Renal and Urinary	6	10	6 (1.1)	8 (1.5)	0.59
Cardiac	8	5	7 (1.3)	5 (0.9)	0.56
Immune System	7	2	7 (1.3)	2 (0.4)	0.18[c]
Metabolism and Nutrition	7	2	5 (0.9)	2 (0.4)	0.45[c]
Neoplasms (benign, malignant and unspecified (including cysts and polyps))	3	5	3 (0.6)	5 (0.9)	0.51[c]
Endocrine	0	4	0 (0)	3 (0.6)	0.12[c]
Blood and Lymphatic System	3	0	3 (0.6)	0 (0)	0.25[c]
Congenital, Familial, and Genetic Disorders	0	2	0 (0)	1 (0.2)	0.50[c]
Hepatobiliary (not including liver enzyme abnormalities)	0	1	0 (0)	1 (0.2)	0.50[c]
Social Circumstances	1	0	1 (0.2)	0 (0)	0.50[c]

[a] Adverse events coded using NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. AE system categories included contributed < 5% each to total number of adverse events.

[b] Data presented as number of participants (% total participants). For participants who reported multiple AEs within a given system category, the most severe AE per subject, per system is presented.

[c] Based on Fisher's exact test.

Abbreviation: GTE, green tea extract.

Table 4

Gastrointestinal Adverse Events[a] by Symptom, Severity in GTE and Placebo Groups

		Total Events (No.)			# Participants (%) with Adverse Events[b]		
		GTE	Placebo	Total	GTE (n=538)	Placebo (n=537)	*P*-value
Adverse Events	Nausea	69	30	99	55 (10.2)	26 (4.8)	0.001
	Indigestion	49	28	77	38 (7.1)	26 (4.8)	0.12
	Diarrhea	26	47	73	24 (4.5)	43 (8.0)	0.02
	Constipation	19	12	31	17 (3.2)	10 (1.9)	0.17
	Vomiting	10	14	24	10 (1.9)	14 (2.6)	0.41
	Increased gassiness	12	11	23	10 (1.9)	9 (1.7)	0.82
	Abdominal/stomach pain	13	11	24	10 (1.9)	11 (2.1)	0.82
	Bloating	8	7	15	8 (1.5)	7 (1.3)	0.78
	Increased acid reflux	11	8	19	10 (1.9)	8 (1.5)	0.64
	Other	18	16	34	16 (3.0)	13 (2.4)	0.58
Grade (Severity)[c]	1	203	161	364	128 (23.8)	110 (20.5)	0.19
	2	31	22	53	25 (4.7)	21 (3.9)	0.55
	3	1	1	2	1 (0.19)	1 (0.19)	1.00[d]
Totals		235	184	419			---

[a] Adverse events coded using NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

[b] Data presented as number of participants (% total participants). For participants who reported multiple gastrointestinal adverse events, the most severe AE per subject, per symptom is presented. Repeated counting occurred for participants reporting more than one GI AE symptom.

[c] Grade: 1=mild; 2=moderate; 3=severe.

[d] Based on Fisher's exact test.

Abbreviation: GTE, green tea extract.

Table 5

ALT Elevation Events[a] by Severity in GTE and Placebo Groups

		Total Events (No.)			# Participants (%) with Adverse Events[b]		
		GTE	**Placebo**	**Total**	**GTE (n=538)**	**Placebo (n=537)**	***P*-value**
		53	4	57	36 (6.7)	4 (0.7)	<0.001
Grade (Severity)[c]	1	39	4	43	22 (4.1)	4 (0.7)	<0.001
	2	7	0	7	7 (1.3)	0 (0)	0.02[d]
	3	6	0	6	6 (1.1)	0 (0)	0.03[d]
	4	1	0	1	1 (0.2)	0 (0)	1.00[d]

[a] ALT elevation listed in “Investigations’ system category in Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

[b] Data presented as number of participants (% total participants). For participants who reported multiple ALT elevations, the most severe elevation per subject is presented.

[c] Grade: 1=mild; 2=moderate; 3=severe; 4=life-threatening.

[d] Based on Fisher’s exact test.

Abbreviation: GTE, green tea extract.