Green Tea Supplementation: Current Research, Literature Gaps, and Product Safety

Benjamin M Meador*, Suzette L Pereira and Neile K Edens

Abstract
This review broadly addresses the impacts of green tea (GT) and its extracts in a number of clinically-important areas, as listed below. It focuses on the available human research, and randomized, controlled trials, where possible.

Body Composition: GT’s effects are not well established, due to the prevalence of conflicting data. It does appear that if GT is to have a positive effect on these outcomes, it likely needs to be in combination with caffeine.

Physical Function and Exercise: A small but consistent body of literature indicates that GT can enhance physical performance. Specifically, it seems capable of acutely enhancing aerobic capacity, and increasing lipid utilization during aerobic activity.

Cardiovascular Disease: Clinical evidence strongly supports reductions in cholesterol levels and improvements in endothelial function with GT intake. In accordance, epidemiological evidence supports a reduction in overall cardiovascular disease risk with regular GT consumption.

Safety: Overall, green tea supplementation at shown-effective dosages appears to be quite safe and associated with very minimal side effects.

Conclusions: GT supplementation is best-supported as a treatment in cardiovascular disease outcomes. It also has potential in sports performance, and possibly—in combination with caffeine—body composition. For most outcomes, there remains a need for well-controlled human interventional trials.

Keywords
Green tea; Epigallocatechin gallate; Clinical effects; Safe dosing

Introduction
Green tea is steeped from the leaves of the Camellia Sinensis plant. While black tea has traditionally been the choice of western culture, green tea is becoming more prevalent, in part due to the popularization of its purported health benefits. GT has been associated with a variety of benefits, including improved body composition, increased exercise performance, cognitive protection and improvement, cardiovascular protection, and anti-cancer effects.

Though black, oolong, and green tea are all derived from the same plant, green tea contains higher concentrations of endogenous polyphenols as compared to black and oolong tea preparations [1]. It is through these compounds—and largely the catechins subgroup—that green tea seems to exert most of its biological effects. Processing advances have allowed isolation of the polyphenol compounds, and in recent years a significant body of literature investigating their isolated effects has developed. Additionally, considerable clinical research is ongoing and upcoming.

In an effort to broadly delineate the known effects of green tea in human nutrition, this review seeks to address the current literature in three main areas: body composition, cardiovascular disease, and cognition. We will seek to give an overview of the support for beneficial effects in these areas, as well as highlight the literature gaps that may present obstacles to future research and clinical usage. Additionally, we address the issues of dosing safety and efficacy. Green tea’s effects in oncology have been examined relatively extensively, and are omitted herein. While some mention of animal studies is made to illuminate mechanistic knowledge, this review is focused on human outcomes. All data is from human trials and studies unless otherwise noted.

Green tea background
The biological effects of green tea seem to be mainly due to the high content of certain polyphenols. As the name implies, polyphenols are a structural class of compounds characterized by the content of numerous phenol (C6H4OH, carboxilic acid) units. The preparation of green tea reduces the oxidation and fermentation of these compounds as compared to black and oolong tea [1]. It should be noted, however, that more processed green tea products—such as decaffeinated, instant, or pre-mixed varieties—have considerably lower polyphenol content than traditionally steeped preparations [2].

The most prevalent among green tea’s polyphenols are a group of compounds called catechins (approximately 25% dry weight) [2]. Of particular interest in green tea are: catechin, epicatechin (EC), gallocatechin (GC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG). EGCG is by far the most abundant, accounting for approximately 60% of total catechin content [2] and is often believed to be the most biologically active [3, 4]. Less prevalent but still considerable are EGC (19%), ECG (13.5%), and EC (6.5%) [2].

Green tea catechins have been consistently shown to have antioxidant properties in vitro, with EGCG being the most potent [3, 4]. Because of its stronger antioxidant properties, EGCG as an isolated extract has been the focus of considerably more research than any other individual catechin. However, due to the fact the EGCG is least bioavailable and that its biological effects have not been shown to be greatly differentiated from those of green tea catechins overall, we have not made significant efforts to give it individual treatment in the current review.

One element one should be wary of in green tea literature is the fact that green tea is naturally caffeinated, and the caffeine content is often not controlled for. This is of minor importance when interested in the effects of green tea per se, but becomes significant when contemplating the translatability to decaffeinated tea preparations or
extracts. Caffeine itself has effects on many of the outcomes of interest to green tea research, and there is evidence of treatment interactions between catechins and caffeine.

Bioavailability and metabolism

The bioavailability of green tea catechins is complex. Upon ingestion they are subject to modifications by various agents at all stages, ranging from salivary compounds to colonic microorganisms. Intact absorption is low, with unabsorbed compounds subject to further intestinal metabolism and potential subsequent absorption. Tissue distribution is not well characterized in humans, though certainly many compounds are known to reach the plasma. Metabolism, biotransformation, and excretion occur fairly quickly, with typical serum half-lives of 2-5.5 hours.

Absorption: Absorption of intact catechins occurs mainly in the small intestine, though there is some absorption in the oral mucosa [5,6]. Data in the literature varies considerably, however it appears that approximately 10-20% of total ingested catechins are absorbed in the small intestine [7,8]. There are significant differences between compounds in respect to intact absorption and plasma appearance. EGCG appears to have the lowest bioavailability, with approximately 1% of the ingested dose appearing in the plasma. ECG, EGC, and EC have considerably higher absorption, with roughly 2, 3.5, and 9% intact appearance, respectively [9,10]. In general, molecularly larger green tea compounds tend to have lower bioavailability than those with smaller molecular weights [9-12].

Maximum concentrations in the plasma are typically reached by 1.5-2.5 hr post-ingestion, though Cmax appears to be delayed with higher dosages [10,13,14].

Distribution: Tissue distribution of absorbed catechins has not been characterized in humans. However, studies in rodents indicate that they are bioavailable to all tissues examined to-date, including brain, heart, liver, lung, kidney, intestines, spleen, pancreas, uterus, ovary, mammary gland, bladder, bone, skin, esophagus, and thyroid [15,16]. There is also in vitro evidence that once in the cytosol, catechins are able to enter the cell nucleus [17].

Metabolism: Immediately upon ingestion, catechins are subject to alteration by salivary compounds. EGCG is subject to degalloylation (forming EGC). Catechins are largely stable in the gastric lumen, with modification being largely limited to the decomposition of oligomers to monomers and dimmers [18,19].

With the rising pH in the small intestine, considerable metabolism and oxidation begins to occur. EGCG has been shown to be more than 75% oxidized after only 5 minutes in intestinal fluid [20], though the extent to which the dimerized products are absorbed is unknown—though likely low, due to their further increased molecular weight. Extensive glucuronidation by UGT enzymes, sulfation by SULT, and O-methylation by COMT also occur during transport to the mesenteric circulation [8,21-26]. Animal work has indicated that only small amounts of intact catechins are likely to reach the portal vein: the majority will be methylated, glucuronidated, and/or sulfated (reviewed [5,27]). Catechins are subject to further methylation, glucuronidation, and sulfation in the liver [26,28], though the extent to which this occurs in vivo has not been characterized.

While direct, single-study examinations have not been published, rough comparison of the total absorptions in the small intestine to intact appearance in systemic plasma would indicate that only approximately 20% of absorbed catechins reach systemic circulation without conjugation or metabolism by either intestinal or hepatic enzymes [7-10].

Catechins that remain unabsorbed upon reaching the large intestine—as well as the metabolites excreted in the bile—are subject to metabolism by microflora, producing small phenolic acids and valerolactones [5]. These compounds have been detected in the plasma, though the extent of their absorption is not known [29].

Investigation has indicated that at least some metabolites are biologically active. Various metabolites have been shown to remain antioxidative, anti-inflammatory, enzyme-inhibitory, and anti-cancerous (reviewed [30]).

Excretion: The excretion of intact catechins from systemic circulation is accomplished rapidly, with plasma half-lives of approximately 2.0-5.5 hours, and becoming undetectable by 24 hours post-ingestion [13]. While EGCG and ECG are present in the urine only in trace amounts, over 90% of urinary excretion of EGC and EC occurs within 8 hours [10,14].

Biliary excretion profiles have not been characterized in humans. However, given that plasma levels of intact catechins and most metabolites are undetectable by 24 hours, it is reasonable to assume that biliary excretion also occurs within that timeframe. Rodent work has indicated that the liver eliminates a large amount of catechins and metabolites through the bile, with only approximately one-half to one-third of the catechins in mesenteric plasma reaching systemic circulation [24].

Of the 80-90% of catechins which pass through the small intestine unabsorbed, the amount that avoids subsequent absorption as microflora metabolites is unknown. The large variety of possible metabolites—in combination with general degradation in the GI tract—would make thorough measurement of total fecal excretion a difficult task.

Effects on Body Composition

A number of studies have been performed examining the impact of green tea on body composition, focusing mainly on the question of whether or not it can reduce body fat. While on balance the literature seems to support green tea having a small effect in reducing bodyweight and percent bodyfat, the data is not undisputed, and overall the literature base is not yet substantial enough to confidently predict outcomes under any specific conditions. Significantly, questions of metabolism are complicated by the fact that green tea (GT) and its extracts (GTE) contain caffeine unless deliberately decaffeinated, and control procedures have been varied in this regard.

There have been a number of human trials indicating a positive effect on body composition and body weight [31-37], ranging from approximately 2.5 kg to 0.5 kg reductions in bodyweight and 1 to 3 cm reduction in waist circumference. However, there is contrasting research that has not found a significant effect [38-41]. There are no obvious methodological differences to differentiate positive- and negative-findings studies. Additionally, approximately half of the studies finding significant effects did not control for the caffeine content of their tea extracts.

The role of caffeine in green tea’s metabolic effects is currently difficult to determine. Studies showing significant effects have been both controlled [34-37,42] and uncontrolled [31,43,44] in regards to caffeine intake. A meta-analysis of RCTs comparing caffeine
treatment to GTE+caffeine concluded that the addition of GTE produced an average weight loss of 1.4 kg [45]. Furthermore, the same meta-analysis indicated that GTE supplementation in the absence of caffeine does not significantly alter bodyweight [45]. Therefore it seems likely that the significant effects seen on bodyweight are due to the combination of GTE and caffeine treatment, though not all trials using this combination have shown positive results [38,39].

In line with the data suggesting that green tea supplementation can decrease fat mass, there have been metabolic studies demonstrating that green tea is able to reduce respiratory quotient—indicating a greater relative contribution of fatty acids [31,42,43]—and increase energy expenditure [42,44]. However—like much of the literature—the results should be interpreted cautiously, as they are not without counter-findings [46,47], and controlling for caffeine content is not a universal protocol.

One possible mechanism by which green tea may be able to effect changes in body composition is through changes in glucose control and insulin sensitivity. Some animal work has indicated that improvements in insulin sensitivity with green tea are due to increased glucose uptake into skeletal muscle, even while uptake is decreased in adipose tissue [48]. However, the effects of GTE supplementation on glucose and insulin outcomes in human subjects is not yet clear, and an area in need of further research. Briefly, improvements in glucose or insulin variables have been shown in both healthy [49,50] and diabetic or prediabetic [51,52] subjects, while a lack of treatment effect has similarly been shown in healthy [53] and diabetic [51,54] or obese [55] subjects. Systematic differences differentiating positive and negative results are not yet apparent in the literature.

**Body composition interaction with exercise**

Maki et al. [37] examined the impact of green tea extract—in beverage form—on body composition in overweight and obese adults participating in a weight-loss oriented exercise program. The control group consumed a beverage of equal caffeine content. It was found that while green tea did not increase overall weight or fat loss over exercise alone, it was associated with a much greater loss of total abdominal fat and subcutaneous abdominal fat. Since abdominal fat is closely tied to metabolic risk, this would imply that—at least in conjunction with exercise—green tea treatment may have metabolic benefits greater than any direct relationship to bodyweight would indicate.

In contrast, Hill et al. also examined body composition during a weight loss-oriented exercise program, but found no treatment effect on body composition. However, the GT treatment was decaffeinated EGCG [40]. Therefore, the results are in line with the suggestion that green tea and its extracts require the combination with caffeine for full metabolic effect.

**Body composition variables: Genetic differences**

The majority of the body composition literature has examined green tea’s effects in overweight or obese Asian subjects. Unfortunately, this data is not necessarily translatable to the Caucasian populations that do not already consume high amounts of green tea but do consume caffeine. Another potential racial confound is the fact that for a given BMI, Asians tend to have a higher percentage body fat (~2-5% at the same BMI) than their Caucasian counterparts [56,57]. Recently, Hursel et al. [58] sought to address these issues through a meta-analysis investigation. They determined that current data suggests a smaller GT treatment effect in Caucasians; however, the significance is difficult to determine, due to the small number of Caucasian studies.

Correspondingly, genetic differences exist in the expression of enzymes that may play important roles in mediating green tea’s effects, though in vivo effects have not yet been mechanistically assessed. Catechol-O-Methyltransferase (COMT) is a large contributor to the enzymatic inactivation of dopamine, epinephrine, and norepinephrine [59], and is present in many tissues of the body, including the brain, GI tract, liver, kidneys, adrenals, heart, and lungs [60,61]. COMT in the liver and intestine can metabolize catechins before they reach systemic circulation.

Individuals of Japanese and Chinese descent tend to carry genes for a more active form of the enzyme. While almost 60% of the Asians are homozygous for the high-activity COMT allele and only 5% homozygous for the low-activity, Caucasians are approximately 25% homozygous for both low- and high-activity alleles [62]. This genetic difference has been shown to be manifested at the level of enzymatic activity [63-66]. There is evidence that inhibition of COMT enzymatic activity is a source of catechins’ effects [42,67] due to increased norepinephrine-induced thermogenesis, in the case of fat loss [42] and so differences in baseline activity may well affect treatment effects.

The question of how COMT activity influences the effects of green tea is mechanistically complicated and not necessarily generalizable across outcomes. Several mechanisms could play a role: catechins’ inhibition of COMT activity, COMT’s metabolization of catechins, and the physiological impact of catechin metabolites via COMT. In outcomes that are direct effects of un-altered catechins, we might expect those with higher COMT levels to have reduced responses, due to more rapid metabolism of those catechins. Alternatively, when the inhibition of COMT by catechins is the source of the effect, the outcome becomes more complicated. Whether those with lower basal COMT activity would be affected by further reduction to a greater or lesser extent is difficult to predict. Finally, the catechin metabolites of COMT have biological effects of their own, which further complicates the impact of COMT genotype.

Conflicting data already exists in the literature in regards to COMT activity and effect size; metabolic data suggest a reduced treatment effect at lower COMT levels [58], while data on endothelial function suggests the opposite [68,69].

**Functional Impacts and Exercise Performance**

In contrast to the rapidly-growing literature base addressing impacts on fat mass, there is little data examining the effects of GTE extract supplementation on muscle mass or performance. To date, only one study has found an effect of GTE on any muscle parameter that is not an interaction with exercise treatment. Shen et al. [70] examined the effects of GTE, Tai Chi exercise, and their combination on leg muscle strength in postmenopausal women, and found that GTE alone improved leg muscle strength by ~50% over six months as measured by wall sit times. This improvement was not significantly increased by the combination with Tai Chi exercise.

On the other hand, a few studies have found an interaction with exercise, specifically with examination of green tea as a potential performance enhancer. One study demonstrated that pretreatment with EGCG (7×135 mg over 48 hr) significantly increased maximal oxygen uptake (0.136 L/min, ~4%) during cycle ergometry in healthy adults [71]. Another group demonstrated that pretreatment with
GTE (3×890 mg polyphenols and 366 mg EGCG over 24 hr) was able to increase fat oxidation during sub-maximal cycle ergometry by 17%-increasing the relative contribution of fat oxidation to total energy expenditure by the same proportion [50]. There is also some weak evidence that pretreatment with EGCG may reduce soreness in response to eccentric exercise [72].

Despite the observed effects on muscle strength and exercise aerobic metabolism, there has not been any support for an increase or preservation of muscle mass with green tea. It is important to note that the majority of the existing literature regarding green tea has been oriented towards either short-term exercise/metabolism outcomes or towards weight loss. These studies are intrinsically biased against positive lean body mass outcomes due to their short durations and/or negative energy balances.

### Mental Health and Cognition

In the last several years there has been a growing body of literature investigating the effects of green tea and green tea catechins on various areas of brain function. Generally the focus has been in two areas: mood and depression or distress, or cognitive impairment with aging. Unfortunately, to date the cognitive data remains almost exclusively epidemiological.

Niu et al. investigated the relationship between green tea consumption and depressive symptoms in Japanese adults older than 70. High green tea consumption (≥ 4 cups/day) was associated with an approximately 50% reduction in risk for mild or severe depressive symptoms, which were present in 34% and 20% of the overall study population, respectively [73]. Similarly, Hozawa et al. [74] examined the relationship between green tea intake and psychological distress as measured by a questionnaire. They found that green tea intake of ≥ 5 cups/day was associated with a 20% reduction in risk for psychological distress in Japanese adults ≥ 40y.

Alternatively, Shimbo et al showed no significant association between mental health and green tea consumption among adult (20-69y) Japanese [75].

In an investigation of cognitive impairment in older (≥ 70y) Japanese subject, Kuriyama et al found that ≥ 2 cups/day habitual green tea consumption was associated with lower risk for cognitive impairment, as measured by the Mini-Mental State Examination (MMSE). Assessment of cognitive impairment with the MMSE is typically made by a cutoff-point, below which the subject is deemed to be impaired. Data was not shown for the absolute change in MMSE score, however risks at higher (slight impairment) and lower (severe impairment) score cutoffs were similarly reduced, suggesting a strong green tea effect. Significant risk reductions were not associated with high black or oolong tea intake, or with coffee intake [76].

A similar study examining Chinese adults (≥ 55y) by MMSE scores also found a significant risk reduction with green tea intake, though in this case they also found black and oolong teas to be protective. Additionally, follow-ups were performed 1-2y later, which indicated that tea intake was also protective against cognitive decline [77]. While already a clinically important parameter itself, reduction of mild cognitive impairment may have further-reaching effects, as cognitive impairment is associated with an approximately 10-fold greater risk of conversion to Alzheimer’s disease as compared to otherwise mentally healthy elderly [78].

All of the above-mentioned data on green tea and cognition is epidemiological and largely cross-sectional. Interventional, clinical data on green tea and cognition is limited to one specific compound present in green tea: the amino acid L-theanine. Theanine is extremely rare in the diet, however—while content is highly dependant on the specifics of preparation—green tea contains on average ~8 mg per 200 ml serving [79]. Park et al. [80] examined the impact of 1440 mg GTE+240 mg L-theanine isolate per day for sixteen weeks on cognitive function in Korean adults with mild cognitive impairment. After sixteen weeks, the treatment group was found to have improved memory and attention as compared to placebo. Additionally, EEG testing indicated that the GTE+theanine treatment elevated brain theta wave activity, an indicator of cognitive alertness. Additionally, Nobre et al. [81] examined the acute effects of a smaller (50 mg) L-theanine dose on brain activity and found a time-dependant increase in alpha wave activity out to 105 minutes post-ingestion, at which time data acquisition was halted. This suggests the potential for increased mental alertness and attention (functional tests were not performed).

Significant shortcomings are immediately apparent with in current literature addressing mental health. Most problematic is the fact that all current GT and GTE studies are cross-sections of subjects who are likely long-term tea drinkers; there is no information on the duration or total consumption necessary to elicit any of these effects. Despite efforts to control for confounding variables, the possibility of incomplete covariate analysis also cannot be ruled out. The clinical, interventional data addressing cognition has focused on L-theanine, which was identified as a compound of interest a-priori, and is not necessarily representative of green tea’s effects as a multi-component compound.

Additionally, all current studies are in adults—typically older—of Asian descent. Similar to the data on body composition, there is reason to believe that there may be racial differences in the response to green tea in regards to cognitive outcomes (see section 3.3 for initial genotype & COMT discussion). As a regulator of dopamine, epinephrine, and norepinephrine levels, the enzyme COMT is positioned to have an impact on cognitive variables, and indeed genetic variation has been very strongly linked to risk for multiple psychological disorders [82-89]. The interactions between green tea catechins and COMT make it quite possible that the genetic differences between Asian and Caucasian populations in regards to COMT expression will lead to treatment effect variations between the two populations.

### Cardiovascular Disease

#### Epidemiological evidence

A considerable number of epidemiological studies indicate that green tea consumption reduces the risk of cardiovascular disease. Blood pressure and hypertension [90,91] and endothelial function and arterial compliance [92] are risk factors that have been shown to be improved in regular green tea drinkers. Additionally, more direct outcomes, such as the development or progression of atherosclerosis [93,94], risk of myocardial infarction [95], and risk of death due to cardiovascular disease [96] have also been found to be improved.

The epidemiological literature is, however, far from uncontested. In 2001, a meta-analysis was published examining the potential variables responsible for variations in green tea’s cardiovascular effects. The most prominent factor in heterogeneity of outcomes was the geographic region in which the study was conducted. Consistently
reduced risk for CHD and myocardial infarction with green tea intake was found in continental Europe, while numerous studies from the United States showed little to no effect on the same outcomes. While green tea did appear to reduce risk for myocardial infarction, results for stroke risk and coronary heart disease were determined to be too variable to fully summarize [97].

More recent follow-up meta-analyses including additional data reexamined the epidemiologic data on stroke risk and determined that both green tea and black tea reduced risk, though green tea was a more potent moderator [98,99]. These analyses found that tea consumption of ≥ 3 cups per day reduced stroke risk between 13% [98] and 21% [99], and was not dependent on geographic region.

Blood pressure – Clinical evidence

There has been one randomized, controlled trial indicating that GTE is able to reduce blood pressure. Nantz et al. [100] demonstrated that three weeks' treatment with decaffeinated GTE (400 mg GTE+200 mg theanine per day) was able to reduce blood pressure by 5 mmHg systolic and 4 mmHg diastolic. Subjects were healthy adults, aged 21-70 years.

However, the inclusion of theanine in the experimental treatment without corresponding controls makes it impossible to determine whether GTE alone would have the same effect. There is evidence from animal research that theanine can reduce blood pressure [101,102], as well as evidence in humans that it can relax the central nervous system [81,103]. Additionally, there is contrasting research indicating that green tea exacerbates the acute (30 minute) pressor response to caffeine ingestion, by 5.5 mmHg systolic and 3.1 mmHg diastolic. This response was non-significant by 60 minutes post-ingestion [104].

In sum, there is no interventional evidence that GTE or GT alone decrease blood pressure, though there is evidence that caffeinated green tea can acutely and transiently increase blood pressure.

Cholesterol levels – Clinical evidence

In contrast to most cardiovascular outcomes with green tea intake, there are actually a large number of high-quality clinical trials which have investigated the effects of green tea intake on blood cholesterol levels, with several being double-blind RCTs with greater than one hundred subjects [34,37,100]. The impact of GT on blood cholesterol levels was recently examined by meta-analysis. This meta-analysis included only clinical trials, and still was able to include 14 studies meeting their selection criteria after the exclusion of 13. The authors found that GT and GTE intake significantly reduced total cholesterol and LDL, but had no significant effect on HDL. The effects of GT on cholesterol were not significantly impacted by the subjects' baseline health status (obese, hypercholesterolemic, healthy, etc.), nor by the type of intervention or dosage of GT or GTE used. The authors concluded that green tea consumption lowers LDL by 2.2 mg/dL, and total cholesterol by 7.2 mg/dL [105].

The mechanisms for the reduction in cholesterol are not fully known, however research in animals suggests that catechins are able to reduce intestinal absorption of cholesterol [106] and upregulate LDL expression in the liver [107,108]. Additionally, in vitro research has shown that catechins are able to inhibit squalene monoxygenase [109], an enzyme of the mevalonate pathway—which may allow them to inhibit endogenous cholesterol synthesis.

In addition to the clinical data demonstrating the ability to reduce LDL and total cholesterol levels, there is also in vitro and ex vivo evidence suggesting that catechins are able to reduce the oxidation of LDL [110,111]. If also effective in vivo, this could have the effect of reducing foam cell formation in atheromas.

Endothelial function – Clinical evidence

The vascular endothelium plays an important part in regulating vascular tone and overall structure, and in fact many other risk factors for cardiovascular disease—such as hypertension, smoking, hypercholesterolemia, and diabetes—have been associated with endothelial dysfunction [112]. The impact of green tea on endothelial function is another area with considerable supporting interventional literature. In healthy adults, green tea supplementation has been found to acutely increase flow-mediated dilation (FMD, a measure of endothelial function) in the brachial artery [113,114]. Additionally, it has been shown to acutely improve endothelial function in smokers [115,116] and patients with coronary artery disease [117], as well as in patients with chronic renal failure after long-term supplementation [118]. Corresponding ex-vivo research has indicated that the catechins epicatechin and EGCG are able to augment endothelium-dependant vasodilation by activation of endothelial nitric oxide synthase [119,120].

Furthermore, while there are many more studies supporting the impact of black tea on endothelial function than there are examining green tea, there is data indicating that the effects of green tea and black tea on endothelial function are not appreciably different [114,121].

The impact of the genetic variations seen in COMT expression on endothelial function has been investigated directly (see 3.3 for initial genotype discussion). Miller et al. compared the GT-induced changes in endothelium-dependant Flow-Mediated Dilation (FMD) of subjects homozygous for the high-activity COMT polymorphism to subjects homozygous for the low activity form. Interestingly, while no significant treatment effect for green tea was found, there was a significant interaction effect for genotype x treatment for the measurement of small vessel tone in the fingertips; those with low-activity COMT showed a greater response to GT. Since this was one only one of several measured variables, the authors conclude that the clinical impact of COMT genotype's interaction with GT on vascular function is likely "modest" [69]. In agreement with this data, another study examining FMD response to green tea found that those individuals with the lowest urinary excretion rate of 4-O-methygallic acid—an expected metabolite of catechins via COMT—had the greatest improvement in FMD with GT treatment [68]. This would suggest that the endothelial response to green tea would—on average—be greater in those of Caucasian vs. Asian descent.

Adverse Events with Supplementation

Green tea supplementation does not appear to be associated with a large number of side effects, and it may be possible to greatly reduce any side effects by simple guidelines such as taking the extract with food, rather than in a fasted state. Currently, the US Pharmacopeia (USP) Dietary Supplements Information Expert Committee (DSI EC) has assigned green tea extracts a class 2 safety rating, indicating that:

“...The DSI EC is unaware of significant safety issues that would prohibit monograph development when the article is used and formulated appropriately, provided there is a warning statement in the labeling section” [122].

Subsequently, the developed monograph is as follows:

“Take with food. Discontinue use and consult a healthcare practitioner if...”
practitioner if you have a liver disorder or develop symptoms of liver trouble such as abdominal pain, dark urine, or jaundice" [122].

Case reports of adverse events
In their recent address of green tea toxicity concerns, the USP has identified Liver damage/toxicity as the primary clinical adverse effect of GTE supplementation. In a review of 216 available case reports involving GTE in the U.S, Australia, and Europe, the USP identified liver toxicity as the primary outcome of concern, and closely addressed 34 related case reports. However, of those 34 reports, GTE was rated a probable cause in only 7. The 7 cases were spread across 6 different brands of GTE [122]. There were no indications that the effects were due to contaminants.

One product of note in the USP report is Exolise, a weight-loss supplement marketed in Europe containing 25% catechins. Exolise was pulled from the market in 2003 (available since 1999) upon fears of liver toxicity in 13 subjects. The estimated incidence of adverse effects was 1 case per 100,000 boxes of product. Upon examination of those reports, the USP assigned probable causality to Exolise in only 2 cases, and medical information that may have pointed to other contributing factors was not fully available in either case [122].

Interventional literature: adverse events and Pharmacokinetics:
The concerns over liver damage stemming from open-market availability have not been mirrored in controlled trial settings. To date, no discovered interventional trial has reported adverse effects concerning liver damage. In fact, two studies have been performed that specifically tracked liver enzymes and function, neither of which found any evidence of adverse effects on the liver [123,124].

The main side effects of note in interventional literature have been reports of either elevated blood pressures or gastrointestinal discomfort and nausea [9,12,13,125]. However, in all of the reports involving BP increases, caffeine was included in the GTE treatment. It may be relevant to note that while gastrointestinal discomfort or nausea may not be serious side effects per se, they could potentially have significant impacts on trials where nutrition and protein balance are important.

Additionally, in almost all cases of gastrointestinal distress, the daily doses of GTE was 800mg or above [9,12,13,125]. In fact, there are no reliable indications in trials literature that caffeine-free GTE dosing below 800mg/day has any adverse effects. Correspondingly, pharmacokinetic research has indicated that plasma concentrations of EGCG begin increasing disproportionately above 800 mg/doses [12,126].

Another effect of note is the timing of supplementation in respect to food intake. It has been shown that maximum plasma concentrations of EGCG are reduced approximately 3.5 times by taking the supplement in conjunction with food vs. a fasted state [9].

Finally, while it may seem prudent to distribute a given dosage throughout the day to achieve the same treatment level while avoiding dangerous spikes in plasma concentrations, work in animals has suggested that two doses within 6 hours may increase tissue—including liver—catechin levels by 2-3 times vs. what would be achieved by a single large dose [16].

Altogether, the available pharmacokinetic information indicates that a single dose <800mg/day, taken with food, is the safest dosing protocol.

Dosing conclusions

- **Body composition**: The combination of body-composition outcomes and adverse event analysis gives a range of approximately 550-800 mg/day GTE where there would be the best possible reasons to expect both efficacy and safety. This equates to about ~165-240 mg/day EGCG (assuming 30% EGCG content), though the efficacy of EGCG alone has not been well examined for these outcomes.

- **Function and Exercise**: While there is little data to recommend any particular GTE dose over another in terms of functionally relevant outcomes, it does appear that EGCG treatment (be it isolated or as GTE) has functional effects at ~165-300 mg/day and higher.

- **Cardiovascular outcomes**: Despite the relatively large number of intervention trials addressing lipid profiles and endothelial function with green tea, the most effective dosage remains difficult to recommend. The vast majority of cardiovascular studies use dosages below 800 mg catechins per day, so there is little to recommend exceeding this upper limit. However, there is no lower-limit (significant effects shown down to ~70 mg acute dose [116]) or dose-responsive trend apparent in the literature. In fact, a meta analysis of GTE and lipid profiles concluded that dose was not a significant factor in effectiveness [105]. On average, cardiovascular literature has used doses of ~550 mg/day.

- **General protocol**: For the best combination of safety and efficacy, we would recommend that GTE supplementation be provided with food, at a dosage of ~550 mg/day. Further, while liver effects have not been strongly implicated in the literature, it is suggested that subjects with known liver pathology or alcohol intake greater than 14 drinks per week [127] be excluded from participation.

An isolated EGCG supplementation dosage is difficult to recommend, as it would be based on a very limited number of trials. Nevertheless, reasonable estimates of ~30% EGCG content in most extracts would indicate that ~165 mg/day—following the same procedures and caveats as GTE—is safe. However, the support for EGCG’s efficacy is minimal when compared to that for multi-catechin extracts, so there seems to be little reason to suggest isolated EGCG supplementation over whole extracts.

A review of 58 currently ongoing or upcoming clinical trials involving EGCG or GTE (as discovered on clinicaltrials.gov, data not shown) indicates that future trials will be pushing the upper limits for supplementation. These trials are/will be using average GTE dosages of 960 mg/day (median 800 mg) and EGCG dosages of 570 mg/day (median 400 mg) in non-cancer trials. Cancer trials are using 985 mg/day (800 mg) and 766 mg/day (1000 mg), respectively.

Conclusion
Overall, the current literature indicates that green tea and its extracts have diverse biological effects, though the extent of those effects is not well determined in all areas. The best-supported interventional outcomes are improvements in cardiovascular disease risk, most significantly in improved lipid profiles and improved endothelial function. Both of these variables are closely associated with overall cardiovascular disease risk. Furthermore, these outcomes can be easily assessed via well-established methods in relatively short time frames—in fact, changes in endothelial function may be seen acutely.
Support for improvements in body composition is complicated by the poorly delineated interactions with caffeine; current data would indicate that the interaction with caffeine is important to improvements in body composition; however the research is not definitive in this area.

There may also be potential for green tea in sports performance. While the literature in this area is very limited to-date, it does appear as though the effects on substrate metabolism seen in body composition research may also carry over to sports performance, leading to a greater utilization of lipid metabolism. Such an effect could be of interest to endurance event performance.

The green tea dosages required to achieve measurable improvements have been consistently shown to be safe and associated with minimal side effects in interventional research. A review of regulatory reactions in Europe has indicated that they may have been overly cautious. Epidemiological evidence also indicates that there are few deleterious side effects to green tea intake.

References


