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Is Green Tea the Panacea We've Been Searching For? A Review of the Scientific Literature on Green Tea and Human Health

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Abstract

There are many claims surrounding the health benefits of consuming green tea, some of which involve its use in the treatment of medical conditions as wide ranging as cancer, diabetes, and neurodegenerative disorders. The desire for the use of non-toxic and natural drugs to treat various diseases makes any health-benefitting claims about green tea and its components important to investigate for their potential public health benefits. I conducted a critical review of the research literature on green tea and its effects on human health and synthesized the results. There is convincing epidemiological evidence pointing to the health benefits derived from consumption of green tea, but National Institutes of Health (NIH)-funded clinical trials are few in number and have produced only modest results. The main biologically active compound in green tea, epigallocatechin gallate (EGCG), does not demonstrate specific binding to biological molecules and varies greatly in its concentration in green tea. EGCG also has a weak, but notable, relationship between dose and maximum plasma concentration in humans; however, most concentrations of EGCG used in laboratory studies are far beyond the physiologically achievable levels. Additionally, there is evidence that high doses of EGCG may lead to liver damage. Finally, green tea polyphenols are implicated in a vast number of interactions, but these are not well understood and suggest the possibility of pan-assay interference. Without clear mechanistic evidence or reliable dosing strategies, it is unlikely that green tea will be suitable for pharmaceutical uses in the treatment of human disease.

Introduction

Green tea is claimed by the news media and scientists alike to be a source of health benefits for many conditions in humans. However, with the supposed health benefits of green tea ranging from ultraviolet light protection to memory improvement to weight management, it can be

difficult to separate fact from fiction. Scientists have a renewed interest in utilizing natural remedies in modern medicine, and nutrition researchers have begun to focus on determining the role of bioactive compounds in the pathology of diseases (Kris-Etherton and Keen 2002). In recent years, the research focus has shifted towards the role of bioactive compounds in the prevention and treatment of diseases (Khan and Mukhtar 2013; Kris-Etherton and Keen 2002; McKay and Blumberg 2002). For many centuries, tea has been considered one of the most beneficial sources of bioactive compounds (Narotzki et al. 2011; Serafini et al. 2011). In 1211, for example, the Japanese Zen priest Yeisai published the book *Kitcha-Yojoki*, translated as "Tea and Health Promotion", describing the pharmaceutical applications of green tea, *Camellia sinensis* Theaceae (Suzuki et al. 2012). Much has changed since 1211, but the public's fascination with tea and its health benefits have remained. Because tea is the most consumed beverage in the world aside from water, even small beneficial health effects in humans could result in significant effects in global public health (Kuriyama et al. 2006; Rimm and Stampfer 2004).

Numerous epidemiological studies provide support for green tea's role in preventing and treating many disorders (Hertog et al. 1995; Iso et al. 2006; Kris-Etherton and Keen 2002; Kuriyama et al. 2006; Mozaffari-Khosravi et al 2013; Odegaard et al. 2008; Sesso et al. 1999; Yang et al 2004). These epidemiological studies suggest a relationship between drinking green tea and positive health outcomes; however, epidemiological studies are not capable of determining if green tea is directly causing these outcomes. While many epidemiological studies provide valuable insight into real-world effects of green tea consumption on human health, many confounding variables exist (Riemersma et al. 2001). These variables include gender, weight, diet, activity, smoking, coffee consumption, genetics, etc. Though epidemiologists work to

control many of these confounding variables, it is not possible to completely control for all of them. A more direct way to evaluate green tea's health benefits is to determine: 1) the specific components in green tea producing the effects, i.e., bioactive molecules; 2) how these bioactive molecules produce the effects, i.e., their mechanism of action; and 3) the availability of these molecules to cells in the body, i.e., their bioavailability. These characteristics can only be evaluated in clinical and laboratory studies.

There are numerous bioactive molecules in green tea, but most attention has focused on polyphenols. Green tea is rich in polyphenols, which are antioxidant compounds capable of neutralizing highly reactive molecules called free radicals (Kim et al. 2014; Quideau et al. 2011). Although best known for their antioxidant properties, polyphenols may have antiviral, antibacterial, and gene regulation properties (Kim et al. 2014; Kozłowska and Szostak-Węgierek 2014). The most studied polyphenol in green tea is epigallocatechin gallate (EGCG) (Williamson and Manach 2005). A recent search for "green tea" in the major biomedical literature database PubMed produced over 5,000 articles, and a search for "EGCG" yielded more than 4,000 articles. A quick scan of the review articles published in 2014 alone revealed studies of green tea within the context of various cancers, infectious diseases, inflammation, oral health, cognitive mood and function, neurodegenerative diseases, and obesity.

The observation of so many different biological effects purportedly arising from the ingestion of green tea raises concerns about the specificity of EGCG (Table 1). Recently, a new classification of chemicals deemed "pan-assay interfering" compounds, or PAINS, has cast doubt upon the usefulness of compounds such as EGCG as potential medical therapies (Baell and Walters 2014). Alternative names for PAINS include "frequent-hitters" and "promiscuous compounds", as they often appear in a variety of unrelated pathways and systems (Bajorath

2014). Effective drugs are characterized by their ability to bind to a specific site on a protein, which thereby induces activation or inhibition of that particular protein (or pathway). Researchers measure the ability of drugs to bind proteins using various assays, but it has been suggested that PAINS are capable of "tricking" these assays into giving false-positive results (Baell and Walters 2014). PAINS may bind to a protein, but they do not bind in a specific location required for drug-like action, and therefore the binding signal may be an artifact and not an indication of specific biological activity (Baell and Walters 2014). EGCG has been flagged as a potential PAIN compound due to its apparent omnipresence in biological systems (Baell and Walters 2014). Some researchers have suggested that plant phytochemicals such as EGCG may act promiscuously in humans by altering membrane protein function and thus merely appear to be pervasively active (Ingólfsson et al. 2014). The pharmaceutical industry has understood for some time the importance of classifying these “bad actors”; however, researchers continue to publish papers ascribing the potential pharmaceutical applications of compounds that do not demonstrate specific biological activity (Baell 2010). Is it possible for one beverage to be a therapy for everything from prostate cancer to sunburn? Or, is it more likely that green tea’s apparent universal application is because it is a PAIN?

In some cases, researchers propose cellular and molecular mechanisms by which green tea may produce a health benefit. EGCG’s classification as an antioxidant, however, only heightens concerns of non-specific interactions not suitable for pharmaceutical drug classification. Antioxidants act to neutralize the harmful effects of reactive oxygen species (ROS), such as peroxides, and reactive nitrogen species (NOS), such as peroxynitrate (Anissi et al. 2013). ROS and NOS contain extra electrons that attack other molecules, which can result in damage to proteins, DNA, etc. (Sullivan and Chandel 2014). Antioxidants, such as EGCG and

other green tea components, neutralize ROS and NOS, and thus act to prevent damage by these molecules (Sullivan and Chandel 2014). Pharmaceutical drugs are categorized in part by their specific binding sites (Baell and Walters 2014); however, antioxidants are not specific in their targets and therefore should not be classified as such.

Regardless of the mechanism of action, much of the scientific literature fails to address the efficacy of green tea as a therapy. For example, the Unites States Department of Agriculture found that concentrations of EGCG in 100 g samples of different green teas varied over 100-fold, suggesting that its reliability as a consumable therapy is dubious at best (United States Department of Agriculture 2013). Scientists conducting research into the mechanisms of action utilized by EGCG often do not address the issue of EGCG's concentration in the blood, which studies show is not highly realted with dose (Ahn et al. 2014; Anita et al. 2014; Audomkasok et al. 2014; Bashir et al. 2014; Delabre et al. 2015; Jeon et al. 2014; Lee et al. 2014a; Miranda-Henriques et al. 2014; Nasri et al. 2013; Ohmori et al. 2014; Saleh et al. 2014; Table 2; Figure 1). Additionally, the concentrations of EGCG examined in laboratory studies using cell cultures and animal models, while meaningful within the scientific community, have little or no meaning to the general public and are generally regarded as far higher than physiologically achievable levels in humans (Lambert and Yang 2003). From a public health perspective, the conclusions drawn from some of these studies are difficult to assess in regard to their application to a broader audience.

In this thesis, I will examine epidemiological, clinical, and laboratory studies investigating green tea's effects on human health. I will also critically evaluate some of the proposed mechanisms of action of green tea required to produce the beneficial results to determine their feasibility within humans. Furthermore, I will assess EGCG's potential

classification as a pan-assay interfering compound. The goal of this thesis is to determine whether green tea's putative health benefits are scientifically supported — epidemiologically, clinically, and biochemically.

Epidemiology of Green Tea Consumption

Epidemiology is the study of the distribution and determinants (causes/risk factors) of morbidity (disease), injury, disability, and mortality within a population (Friis 2010). Epidemiologists use surveillance and descriptive studies to determine and track the distribution of health problems and analytical studies to investigate determinants (Friis 2010). Descriptive/surveillance epidemiology aims to characterize the amount and distribution of health conditions within a population, relying on the systematic collection, analysis, and distribution of information pertaining to the disease occurrence (Friis 2010). Analytic epidemiology focuses on studying the determinants of a disease within a population, examining the etiological (causal) factors linking exposures and health conditions (Friis 2010). Both of these epidemiological approaches allow a comprehensive examination of the incidence of a health condition within a community and provide information for intervention.

Several epidemiological studies suggest that drinking green tea does have beneficial health effects. One of the largest epidemiological studies on the health benefits of green tea is the Ohsaki Study. From 1994 through 2005, the Ohsaki Study looked at the relationship between green tea and mortality for 40,530 healthy Japanese adults aged 40 to 79 from the Miyagi Prefecture in northeastern Japan (Kuriyama et al. 2006). A previous survey had reported that 42% of people in the Miyagi Prefecture regularly drank five or more cups of green tea daily (Tsubono et al. 2001). The Ohsaki Study was designed as a prospective cohort, in which similar individuals who differ in a certain factor, in this case green tea consumption, are followed over

time to determine the effects of green tea consumption on a certain outcome, in this case mortality. The Ohsaki Study found that those who reported drinking five or more cups of green tea daily were significantly less likely to die during the period of observation than those who drank less than one cup per day (Kuriyama et al. 2006).

One of the most prevalent claims relating to green tea's health benefits is its ability to lower the risk for cardiovascular disease. Cardiovascular disease refers to conditions relating to the heart and the blood vessels and includes disorders such as arrhythmia, atherosclerosis (buildup of plaque in arteries), hypertension, congenital heart defects, stroke, and heart attack (Phinikaridou et al. 2013). As the leading cause of death in the United States, cardiovascular disease is responsible for one in every four deaths and costs $108.9 billion annually in lost labor and treatment (Heidenreich et al. 2011; Murphy et al. 2013). According to the Centers for Disease Control and Prevention (CDC), 49% of Americans have at least one of the three major risk factors for cardiovascular disease: high blood pressure, high LDL cholesterol, and smoking (Valderrama et al. 2011). There are many epidemiological studies that focus on the role of green tea in improving cardiovascular health.

The Ohsaki Study noted a decrease in deaths due to cardiovascular disease in green tea drinkers. Women who drank five or more cups (1 cup = 100 mL) of green tea per day were 31% less likely to die from cardiovascular diseases during the observation period than those who drank less than one cup of green tea per day (Kuriyama et al. 2006). Another prospective cohort study, The Seven Countries Study, followed sixteen cohorts over twenty-five years starting in 1960 and found that there was an inverse relationship between green tea intake and death due to coronary heart disease (Hertog et al. 1995). The Boston Area Study found that the risk of heart attack was reduced by 44% in those who drank one or more cups of green tea per day as

compared to non-green tea-drinking controls (Sesso et al. 1999). Finally, a study conducted in Taiwan found that consumption of between 120 mL and 599 mL of green tea daily reduced the development of hypertension by 46% and that drinking over 600 mL daily reduced the risk of hypertension by 65% (Yang et al. 2004). Each of these statistically significant results strengthens claims that green tea is capable of reducing the incidence of cardiovascular disease.

As a strong risk factor for cardiovascular disease, diabetes has also been extensively examined epidemiologically in the search for new, natural therapies. Diabetes mellitus results from an inability to respond to and/or produce insulin, the hormone responsible for the uptake of glucose by cells (Philippe and Raccah 2009). Type 1 diabetes is an autoimmune disorder, whereas Type 2 is the progressive development of insulin resistance and secretion defects leading to varying degrees of decreased β-cell function in the pancreas (Cnop et al. 2005; Liese et al. 2013; U.K. Prospective 1995). Due to increased longevity and obesity, some researchers predict that the global incidence of Type 2 diabetes, currently at 7%, will increase to 15% by 2030 (Boyle et al. 2010; Philippe and Raccah 2009; Wild et al. 2004). In the United States, 9.3% of the population suffers from diabetes and 95% of new cases in adults are Type 2 diabetes (Centers for Disease Control and Prevention 2014).

Epidemiological studies on diabetes vary in their conclusions on the effectiveness of green tea as a potential therapy or preventative. One study of 17,000 Japanese men and women found that drinking six or more cups of green tea daily led to a 33% reduced risk of developing Type 2 diabetes (Iso et al. 2006). Another study found that drinking three cups of green tea daily for four weeks decreased blood pressure in 39.6% of Iranian Type 2 diabetes patients (Mozaffari-Khosravi et al. 2013). In contrast, the Singapore Chinese Health Study of over 36,000 participants saw no association between the consumption of more than one cup of green tea daily

and a reduced risk for Type 2 diabetes (Odegaard et al. 2008). Therefore, it is not possible at present to say whether green tea is effective at reducing risk for Type 2 diabetes, and additional research will be necessary to elucidate the potential links between green tea and diabetes.

Cancer is another area in which many epidemiological investigations regarding green tea's health benefits have been conducted. Cancer results from the accumulation of mutations in genes that regulate cell proliferation (Samuels et al. 2011). These mutations lead to uncontrolled cell division without the normal checkpoints and regulation (Alberts et al. 2007). These mutations may be inherited, increasing one's risk of cancer, or occur spontaneously as the result of environmental exposure to tobacco or other chemical carcinogens, viruses, radiation, etc. (O'Connor et al. 2011). One nine-year study, conducted in Japan in the 1990s, found that females were statistically less likely to develop cancer of any type if they drank green tea regularly; however, the effect was only significant in those drinking on average ten or more cups of green tea daily (Imai et al. 1997).

In 2013, there were 234,580 new cases of breast cancer reported in the United States along with 39,620 deaths (Rebecca and Jemal 2013). Many epidemiological studies suggest that green tea may have a beneficial effect for breast cancer patients (Li et al. 2014). A 2014 meta-analysis (the application of statistics to data collected and pooled from multiple studies) from five case-control studies showed a statistically significant 19% reduction in breast cancer risk among green tea drinkers (Li et al. 2014). However, an earlier meta-analysis of eight studies concluded that there was not enough statistical support to suggest that green tea had any effect on reducing breast cancer incidence (Seely et al. 2005). While interesting, these studies are not conclusive and further research will need to be conducted into the relationship between green tea and breast cancer.

There is some compelling epidemiological evidence suggesting that green tea may provide therapeutic benefits in certain health conditions. While epidemiological studies are useful to observe effects in the context of daily life, it is impossible to control for all variables. For example, many of the epidemiological studies conducted on green tea take place in Asia. As a result, differences between these Asian populations and other populations around the world in regards to genetics, diet, microbiota, etc. are impossible to completely control for in epidemiological studies. These differences can confound efforts to analyze green tea's impact in other populations. The next logical step in evaluating green tea's efficacy as a therapy is to conduct clinical trials.

Clinical Trials on Green Tea as a Therapy

Clinical trials are prospective studies looking at the effect of an intervention — such as a drug, surgical procedure, diet, exercise regime, etc. — on human health (Friedman et al. 2010). An ideal clinical trial is one that has the following characteristics: 1) it is randomized — people are assigned to the intervention or control group in a random fashion; and 2) it is double-blind — neither the participants nor the investigators know to which group the participant was assigned (Friedman et al. 2010). In the United States, a clinical trial funded in part by the National Institutes of Health (NIH) and/or other government institutions is the gold standard in quality assurance. Currently, there are only six completed, NIH-funded clinical trials studying the efficacy of green tea as a preventative or therapeutic in various disorders — prostate cancer, chronic obstructive pulmonary disease, human papillomavirus (HPV), osteoporosis, chronic lymphocytic leukemia, and multiple sclerosis. Only three of these studies — examining HPV, osteoporosis, and chronic lymphoid leukemia — have published their results.

Cervical cancer is the most common gynecological malignancy globally (Garcia et al. 2014). Human papillomavirus (HPV) infection is implicated in greater than 99% of all cervical cancer cases (Bosch and de Sanjosé 2003). Previous studies suggested that treatment with green tea supplements might accelerate clearance of HPV infection (Ahn et al. 2003; Tatti et al. 2008). In one clinical trial, Garcia et al. (2014) investigated the effects of Polyphenon E, a concentrated green tea supplement, on prevention of cervical cancer in women with pre-cancerous growth as a result of HPV infection. Ninety-eight women were enrolled in the study, randomly sorted into the Polyphenon E group or the placebo group, and followed for four months. The study found no evidence that Polyphenon E treatment promoted the clearance of HPV infection (Garcia et al. 2014).

Osteoporosis is a degenerative bone disease characterized by lower bone density, which increases the risk for fractures and breaks (National Institutes of Health 2001). This condition causes an estimated 1.5 million fractures annually in the United States at a cost of $20 billion per year (Cooper et al. 2011; Cummings and Melton 2002). Postmenopausal women are four times more likely to develop osteoporosis than other populations because of a decrease in estrogen levels (Looker et al. 2010). A clinical trial conducted by Shen et al. (2012) enrolled one hundred and seventy-one postmenopausal women with osteopenia (lower than normal bone mineral density and therefore at risk for osteoporosis) to determine whether intervention with green tea supplements and an exercise regime with tai chi would improve their bone health. There were four study groups: 1) starch placebo control; 2) green tea supplement (500 mg/day); 3) placebo and tai chi for 60 minutes, three times per week; and 4) green tea supplement and tai chi (Shen et al. 2012). The researchers measured calcium metabolism through parathyroid hormone levels, muscle strength, and the serum levels of two bone turnover markers — bone-specific alkaline

phosphatase (BAP), which is indicates good bone density, and tartrate-resistant acid phosphatase (TRAP), which indicates poor bone density (Shen et al. 2012). Over the course of six months, they observed improved levels of parathyroid hormone and BAP, an improved BAP/TRAP ratio, and increased muscle strength due to the combination of green tea supplementation and tai chi (Shen et al. 2012). On the basis of this study, green tea supplementation alone improved BAP levels within one month, improved the BAP/TRAP ratio within three months, and increased muscle strength within six months. These results suggest that green tea (and tai chi) may be effective at maintaining bone mineral density in postmenopausal women (Shen et al. 2012).

Chronic lymphocytic leukemia is the most common form of leukemia, with 15,000 new cases and 5,000 deaths annually in the United States (Nabhan and Rosen 2014). Many studies suggest that green tea has a therapeutic effect for leukemia and lymphoma patients (Frankenfeld et al. 2008; Kuo et al. 2009; Naganuma et al. 2009; Zhang et al. 2008). In this study, forty patients with asymptomatic, early stage chronic lymphocytic leukemia received Polyphenon E twice daily (Shanafelt et al. 2013). Following six months of treatment, the researchers saw significant declines in absolute lymphocyte count and lymphadenopathy, signs that the cancer was not progressing, in 70% of their patients (Shanafelt et al. 2013). These results suggest that green tea supplements may be effective at preventing the progression of chronic lymphocytic leukemia in early stage patients.

While the trials discussed above suggest that green tea may play a role in maintaining bone mineral density and preventing the progression of leukemia, the mechanism by which green tea (or green tea supplements) accomplishes this remains unknown. Clinical trials are better at controlling variables than epidemiological studies, which often rely on self-reporting; however, clinical trials cannot completely eliminate confounding variables and/or compliance issues.

Clinical trials are currently the best way to measure drug safety and efficacy. The results of these studies, while modest, are somewhat encouraging for green tea's future as a clinical therapy.

Biochemistry of Green Tea

The United States Food and Drug Administration (FDA) does not require that the mechanism of action be understood for drugs before they enter into a clinical trial (Nature Medicine 2010). An editorial in *Nature Medicine*, one of the top international medical journals, argues that lack of knowledge about drug targets and mechanisms hinders the ability to prescribe drugs in a maximally beneficial manner (Nature Medicine 2010). Within green tea, there are fifteen active polyphenols known to interact with at least 200 different targets in humans, but the mechanisms are not well categorized (Figure 2). These targets can be further organized into seven disease groups, but without clearly defined mechanisms it is impossible to assess green tea's effects within these categories (Figure 2). For example, there are nine protein targets within the disease group diabetes, but how green tea polyphenols interact with these proteins and produce medically beneficial effects is not known (Figure 2). I present below two examples of proposed mechanisms that will elucidate the complexity and the ill-defined nature of this research.

With respect to cardiovascular disease, researchers have investigated many different proposed mechanisms for EGCG's role in disease control and prevention. Some scientists have highlighted the ability of green tea to reduce the risk of cardiovascular disease by acting as an anti-thrombotic, anti-oxidant, anti-hypertensive, anti-inflammatory, anti-proliferative, anti-diabetic, and anti-mutagenic (Babu and Liu 2008; Basu and Lucas 2007). For example, in terms of anti-thrombotic action, there is a proposed interaction of EGCG with the enzyme plasminogen activator inhibitor-1 (PAI-1), a key molecule in the formation of a thrombus (Peng et al. 2008; Rijken and Lijnen 2009; Vaughan 2005). High levels of PAI-1 have been linked to an increased

risk for thrombus formation because they preclude the degradation of the extracellular matrix — the web of fibers and associated fluids between cells — by plasmin (Gils and Declerck 2004). Elevated PAI-1 has been demonstrated in a number of conditions including heart attack, coronary artery disease, deep vein thrombosis, and atherosclerosis (Declerck and Gils 2013). EGCG has been shown to hinder the action of PAI-1 in human cell cultures and this mechanism is thought to reduce the risk of atherosclerosis by inhibiting thrombus formation following the rupture of plaque built-up on the arterial wall (Cale et al. 2010; Cao et al. 2013). Thus, inhibition of PAI-1 by EGCG would reduce the risk of thrombus formation.

As with cardiovascular disease, diabetes research has uncovered multiple potential mechanisms of action for how EGCG may act upon the endocrine system, metabolism, redox states, and various cell types to reduce the incidence and impact of Type 2 diabetes and obesity (Kao et al. 2006). For example, one research group used a diabetic mouse model to examine EGCG's effect on glucose tolerance (Ortsäter et al. 2012). After ten weeks, the fasting blood glucose levels for the control group rose to 14.7 mM and the EGCG supplemented mice saw a concentration of 9.3 mM, a statistically significant drop (Ortsäter et al. 2012). However, mice treated with a current diabetic drug — rosiglitazone — had a fasting blood glucose level of only 4.0 mM after ten weeks (Ortsäter et al. 2012). EGCG is less effective than rosiglitazone, but still produced a statistically significant drop in blood glucose levels in mice, and EGCG may prove to be a less toxic and cheaper option.

Developing a comprehensive mechanistic characterization of EGCG and the other compounds in green tea is crucial in determining whether or not green tea will prove an effective therapy for any health conditions. However, the lack of consensus in the literature makes it challenging to identify the truly promising actions. In addition, the concentrations of EGCG

required to achieve even minimally beneficial effects for both atherosclerosis and diabetes are large and not reasonably achieved through the consumption green tea alone — the most effective dose of EGCG in the atherosclerosis study described above was 50 μM and in a cell-culture diabetes study was 10 μM (Table 2, Figure 1; Cao et al. 2013; Kim et al. 2013). In humans, the largest dose of EGCG for which data are available — the equivalent of at least 180 cups of green tea, assuming a generous 10 mg of EGCG per cup — only produced a maximum plasma concentration of just over 6 μM (Table 2, Figure 1). Also, as discussed earlier, the amount of EGCG in green tea can vary dramatically, which raises a number of questions regarding effective dosing (United States Department of Agriculture 2013).

The proposed mechanisms discussed above do not begin to scratch the surface of the potential mechanisms and targets in the literature of EGCG and green tea within the vast array of human disorders in which it is implicated (Figure 2). Given the numerous potential mechanisms involved in the cardiovascular system and diabetes, EGCG and other components in green tea seem to appear everywhere researchers look — suggesting that EGCG may qualify for classification as a PAIN.

The Bioavailability of Green Tea

Bioavailability is a measure of the amount of a drug that enters into circulation — the higher a drug's bioavailability, the greater the drug's effectiveness (Chow and Liu 2009). Bioavailability falls under the umbrella field of pharmacokinetics — the study of the fate of drugs upon administration, for example how much of the drug ends up in circulation or is lost as waste (Shargel et al. 2012). There have been numerous studies on the bioavailability of polyphenols such as EGCG (Table 2, Figure 1), and they do no appear to be readily bioavailable in the body for reasons that are not completely understood (Manach et al. 2004). An important measure of

bioavailability is the C_{max} of a drug, which is the maximum concentration that a drug reaches in blood plasma (Urso et al. 2002). Pharmacokinetic studies conducted with green tea show a large variability in the C_{max} of EGCG, ranging from 0.02-6.35 μM in blood plasma (Table 2, Figure 1). The correlation coefficient, r, is a measure of the strength of a relationship between two variables — the closer the r value is to 1, the stronger the relationship; whereas, another measure of the relationship between variables, the coefficient of determination, r^2, looks at the predictability of changes in one variable producing consistent changes in another variable— an r^2 value closer to 1, means that changes in the independent variable (in our case dose of EGCG) are a better predictor of changes in the dependent variable (in our case C_{max}) (Gerstman 2014). On the basis of a linear regression analysis, there is a positive relationship between dose of EGCG and plasma concentration ($F_{1,24} = 28.18$; p-value ≤ 0.001; $r = 0.73$; $r^2 = 0.54$; Figure 1), but the removal of three clear outliers noticeably reduces this relationship ($F_{1,20} = 11.66$; $p = 0.003$; $r = 0.61$; $r^2 = 0.37$). This variability of EGCG's bioavailability is a challenge when attempting to provide reliable dosing.

The less than ideal relationship between dose and plasma concentration may be related to the variable amounts of EGCG among similar green tea doses. The USDA Database for the Flavonoid Content of Selected Foods found that brewed green teas have anywhere between 2.3 mg and 203 mg EGCG per 100 g serving (United States Department of Agriculture 2013). This variability in the amount of EGCG further suggests that green tea, as a beverage, may prove ineffective as a medicinal therapy. Even with the generous assumption of 10 mg EGCG per cup of tea, an unrealistic amount of green tea would be required to achieve the necessary physiologically levels to see any benefit, as noted in the previous section. It appears impossible for any individual to drink enough green tea to significantly improve their health outcomes.

Green Tea and Liver Damage

Given the studies examined thus far, it does not seem possible for the average human to attain the necessary concentrations of EGCG to experience beneficial health outcomes from drinking green tea alone (Table 2, Figure 1). Thus, it is reasonable to assume that if EGCG is to be used as a drug it will most likely be in the form of a concentrated supplement containing high doses of EGCG. However, there are numerous studies in which researchers have found that high doses of EGCG can cause liver damage in both humans and rodents (Chen et al. 2010; Emoto et al. 2014; Galati et al. 2006; Gallo et al. 2013; Goodin 2006; Lambert et al. 2010; Mazzanti et al. 2009; Molinari et al. 2006; Patel et al. 2013; Salminen et al. 2012; Shanafelt et al. 2013). Some of these studies describe only a single case and/or potential interference by other medications (Emoto et al. 2014; Mazzanti et al. 2009), while others involved high concentrations of EGCG and long-periods of exposure (Emoto et al. 2014). All drugs have toxic concentrations; however, at present, the concentration of and length of exposure to EGCG that would lead to liver damage is unknown (Emoto et al. 2014). The potential for harmful side effects following prolonged exposure and/or high doses — greater than 400 mg EGCG per dose, or about 20 cups of green tea, in humans typically for over a month — raise concerns over whether EGCG could ever be used for therapeutic purposes (Emoto et al. 2014).

Conclusions: Green Tea, Panacea or PAIN?

Is green tea a panacea or a PAIN? Scientists really do not know. The research into green tea's role as a drug is burgeoning, conflicting, and inconclusive. There is strong epidemiological evidence from multiple large studies suggesting that drinking green tea improves health outcomes of certain populations (Hertog et al. 1995; Iso et al. 2006; Kris-Etherton and Keen 2002; Kuriyama et al. 2006; Mozaffari-Khosravi et al 2013; Odegaard et al. 2008; Sesso et al.

1999; Yang et al 2004). However, clinical trials funded by the National Institutes of Health are very few in number and demonstrate only modest results (Garcia et al. 2014; Shanafelt et al. 2013; Shen et al. 2012). The bioavailability of EGCG and other green tea polyphenols is poorly understood (Manach et al. 2004), and the wide range of EGCG present in green tea raises concerns that the dose is not consistent between cups (United States Department of Agriculture 2013). Laboratory studies often involve large doses of concentrated EGCG that are well beyond the amounts that could be consumed by ingestion and there are some warning signs that large doses of EGCG may lead to liver damage (Emoto et al. 2014; Lambert and Yang 2003). Finally, there is concern about the specificity of EGCG and other polyphenols found in green tea, as many of them may turn out to be pan-assay interfering compounds (Baell 2010).

The health claims regarding green tea made to the general public are clearly over-stated. While epidemiological studies look promising, clinical and laboratory trials to date are not compelling, requiring large doses and producing poorly defined benefits. Enjoying a few cups of green tea daily will not harm you, but it probably will not save you from cardiovascular disease, cancer, diabetes, or any other disease. In the absence of convincing mechanisms and consistent dosing, it is difficult to see green tea, or any of its components, rising to pharmaceutical status.

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Table 1. Recent research studies involving green tea and health.

Study	Organism/Cells Examined	Disease/Condition	Discusses Mechanism	Discusses Bioavailability	Discusses Dose*
Fatemi et al. 2014	Rats	Burns	No	N/A, topical	No
Neturi et al. 2014	Humans	*Streptococcus mutans* count in mouth	No	N/A, oral rinse	No
Lee et al. 2014b	Mice	Wrinkles	No	N/A, topical	No
Ohmori et al. 2014	Humans	Coronary Artery Disease	No	No	7 cups per day
Liu et al. 2015	Human Liver Cells in Culture	Cholesterol Metabolism	Yes	No	No
Anita et al. 2014	Cariogenic Bacteria in Culture	Antibiotic Properties	No	N/A	No
Jiang et al. 2014	Human Osteosarcoma Cells in Culture	Osteosarcoma	Yes	No	No
Delabre et al. 2015	Humans	Influenza	No	No	Two cups per week minimum
Audomkasok et al. 2014	Mice	Malaria (*Plasmodium berghei*)	No	No	No
Ahn et al. 2014	Rats	Cisplatin-Induced Nephrotoxicity	No	No	No
Huang et al. 2015	Rabbits	Autologous Chondrocyte Implantation	Yes	No	No
Gu et al. 2014	Rats	Chronic Unpredictable Mild Stress-Induced Cognitive Impairment	Yes	No	No
Liu et al. 2014	Human Aortic Smooth Cells in Culture	Atherosclerosis	Yes	No	No
Khan et al. 2014	Rats	Doxorubicin-Induced Cardiotoxicity	Yes	No	No
Nasri et al. 2013	Rats	Contrast Media-Induced Acute Renal Damage	No	No	No
Suthar et al. 2014	Human Erythrocytes in Culture	Bisphenol A-Induced Oxidative Stress	Yes	No	No

Table 1 (continued). Recent research studies involving green tea and health.

Study	Organism of Study	Disease/Condition	Discusses Mechanism	Discusses Bioavailability	Discusses Dose*
Jeon et al. 2014	Bacteria from Human Skin Wounds in Culture	Bacterial (*Pseudomonas aeruginosa* and *Escherichia coli)* Infection of Skin Wounds	No	No	No
Bashir et al. 2014	Bacterial Cultures	Antibacterial	No	No	No
Miranda-Henriques et al. 2014	Rats	Nonalcoholic Steatohepatitis	No	No	No
Lodhi et al. 2014	Rats	Chronic Ethanol-Induced Hepatotoxicity	Yes	No	No
Chakraborty et al. 2014	Rats	Cyclophosphamide-Induced Myocardial Damage	Yes	No	No
Zhao et al. 2014	Rat Embryo Spinal Cord Neurons in Culture	Spinal Cord Neuronal Oxidative Damage	Yes	No	No
Shin et al. 2014	Rats	Postsurgical Adhesions	Yes	No	No
Saleh et al. 2014	Human Blood Cells from Breast Cancer Patients in Culture	Peripheral Blood Mononuclear Cells Proliferation in Breast Cancer	No	No	No
Lee et al. 2014a	Human Retinal Pigmented Epithelial Cells in Culture	Ocular Angiogenic Disease	Yes	No	No

* In public health relevant units such as ounces, cups, or grams of tea leaves.

Table 2. The varied bioavailability of EGCG.

Amount of EGCG	C_{max} in Plasma	Study/Review
37 mg	0.020 μM	Warden et al. 2001*
50 mg	0.260 μM	Ullmann et al. 2003*
63 mg	0.330 μM	Unno et al. 2005
67 mg	0.170 μM	Lee et al. 2002
75 mg	0.080 μM	Del Rio et al. 2010
100 mg	0.410 μM	Ullmann et al. 2003*
105 mg	0.055 μM	Stalmach et al. 2009
110 mg	0.260 μM	Yang et al. 1998
112 mg	0.125 μM	Williamson et al. 2011
134 mg	0.080 μM	Renouf et al. 2010
200 mg	0.160 μM	Chow et al. 2001*
200 mg	0.710 μM	Ullmann et al. 2004*
200 mg	0.680 μM	Ullmann et al. 2003*
200 mg	0.150 μM	Meng et al. 2002*
214 mg	0.080 μM	Henning et al. 2004
219 mg	0.710 μM	Yang et al. 1998
329 mg	0.700 μM	Yang et al. 1998
400 mg	0.240 μM	Chow et al. 2001*
400 mg	1.100 μM	Ullmann et al. 2004*
400 mg	1.240 μM	Ullmann et al. 2003*
600 mg	0.370 μM	Chow et al. 2001*
800 mg	0.960 μM	Chow et al. 2001*
800 mg	4.950 μM	Ullmann et al. 2004*
800 mg	2.100 μM	Ullmann et al. 2003*
1200 mg	0.113 μM	Lee et al. 1995
1600 mg	6.350 μM	Ullmann et al. 2003*

*Found in: Feng 2006

Figure Legends

Figure 1. The relationship between C_{max} and EGCG dose in humans, based on data obtained from the twenty-six studies listed in Table 2 ($r = 0.73$, $r^2 = 0.54$ for all studies; $r = 0.61$, $r^2 = 0.37$ following removal of outliers, indicated by black diamonds).

Figure 2. The main targets for green tea polyphenols in humans. Fifteen green tea polyphenols (diamonds) are linked to two-hundred protein targets (circles) via lines (grey), which are divided into seven disease categories (from Zhang et al. 2014).

Figure 1

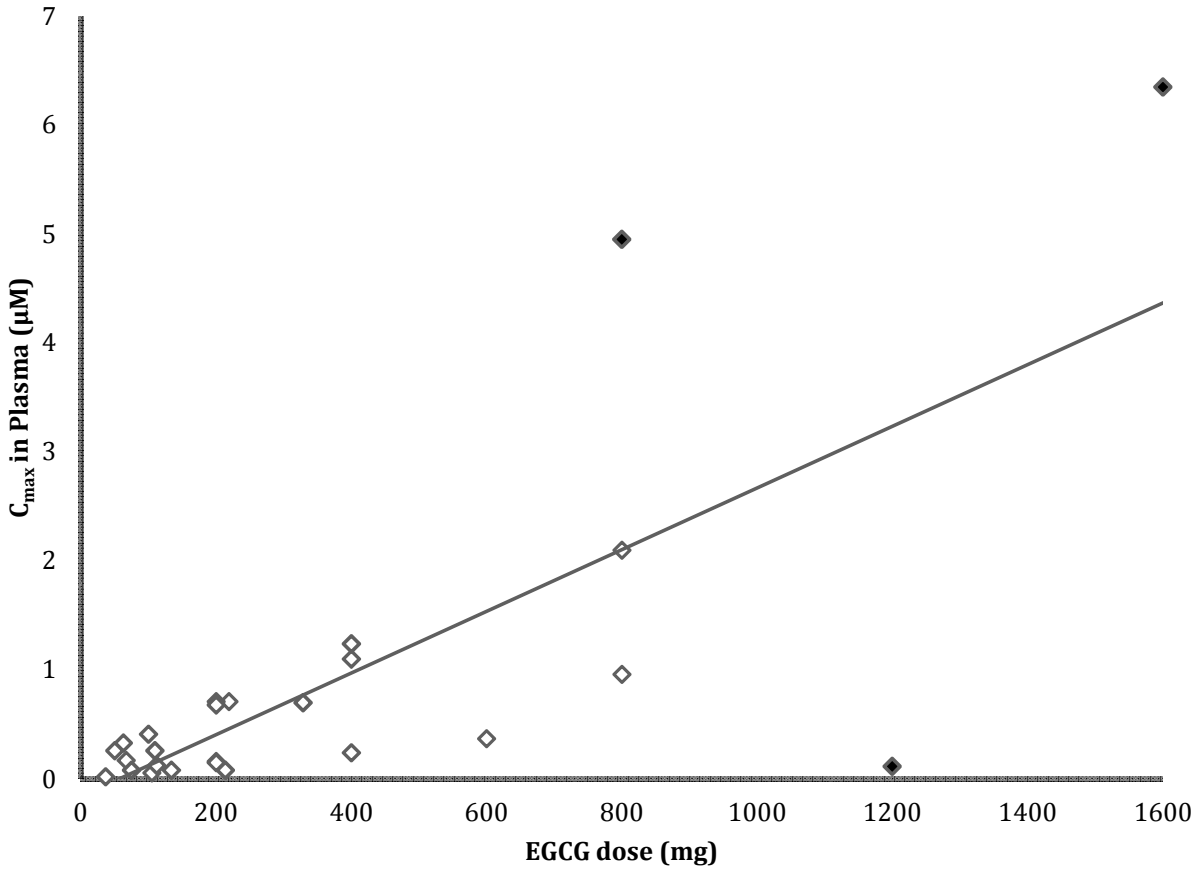
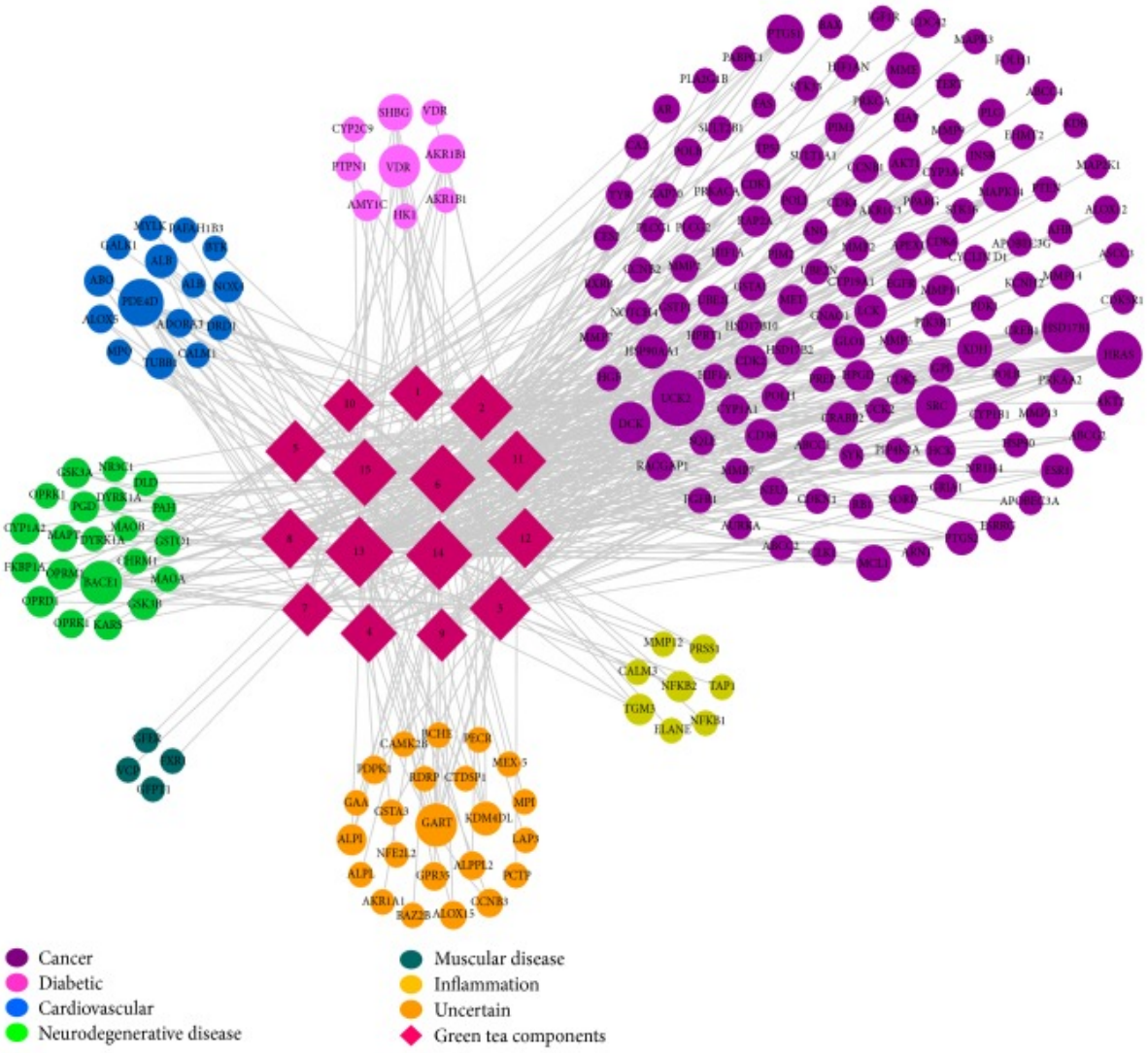

7
6
5
4
3
2
1
0
C_{max} in Plasma (µM)
0
200
400
600
800
1000
1200
1400
1600
EGCG dose (mg)

Figure 2


Cancer
Diabetic
Cardiovascular
Neurodegenerative disease
Muscular disease
Inflammation
Uncertain
Green tea components