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Green tea polyphenols for prostate cancer chemoprevention: A translational perspective

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Abstract

Every year nearly 200,000 men in the United States are diagnosed with prostate cancer (PCa), and another 29,000 men succumb to the disease. Within certain regions of the world population based studies have identified a possible role for green tea in the prevention of certain cancers, especially PCa. One constituent in particular, epigallocatechin-3-gallate also known as EGCG has been shown in cell culture models to decrease cell viability and promote apoptosis in multiple cancer cell lines including PCa with no effect on non-cancerous cell lines. In addition, animal models have consistently shown that standardized green tea polyphenols when administered in drinking water delay the development and progression of PCa. Altogether, three clinical trials have been performed in PCa patients and suggest that green tea may have a distinct role as a chemopreventive agent. This review will present the available data for standardized green tea polyphenols in regard to PCa chemoprevention that will include epidemiological, mechanism based studies, safety, pharmacokinetics, and applicable clinical trials. The data that has been collected so far suggests that green tea may be a promising agent for PCa chemoprevention and further clinical trials of participants at risk of PCa or early stage PCa are warranted.

Keywords

Green tea; EGCG; Polyphenol; Chemoprevention; Prostate cancer

Introduction

In 2008 there will be an estimated 186,320 new cases of prostate cancer (PCa) diagnosed and 28,660 deaths reported (Jemal et al., 2008). On a worldwide scale there is a distinct geographic distribution of PCa with the highest rates occurring in “Western countries” (i.e. United States, Australia, Western Europe) and the lowest rates found in Asia. The process of PCa development will generally begin decades before it is diagnosed and is the result of genetic as well as epigenetic modifications that alter normal glandular epithelium into pre-neoplastic lesions and eventually to an invasive carcinoma. There is often a perception that cancer is genetic, however,

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less than 10% of PCa has been shown to be inherited suggesting that a variety of genetic and environmental factors may be important contributions to PCa development (Syed et al., 2007). What is becoming increasingly evident is that dietary constituents have a unique ability to target multiple deregulated signaling pathways while allowing normal processes to continue. This has led many epidemiologists to suggest the significance of lifestyle and dietary choices in the development of PCa. To further emphasize the role of lifestyle in PCa development, migratory studies have found that Asian men who relocate to the United Sates and adopt a western lifestyle, have a significantly higher risk of PCa when compared to their native Asian counterparts (Shimizu et al., 1991; Lee et al., 2007). One strategy for cancer control, especially suited for PCa, is chemoprevention which is the use of naturally (e.g. dietary) occurring or synthetic agents as a way to prevent, delay, or slow the process of carcinogenesis. From a clinical perspective PCa may be an ideal disease state for chemoprevention due to its diagnosis in men over the age of 50, suggesting that even a modest delay will significantly reduce the incidence of PCa. Further compelling evidence to support the study of dietary components is that certain populations, most notably, the Asian population appear to have the lowest risk of developing PCa and may be the result of consuming specific dietary constituents daily over many years.

For nearly five thousand years tea (*Camellia sinensis*) has been consumed by the Chinese and other Asian populations making it the most consumed beverage in the world next to water. For practical purposes we will define tea as a beverage that is prepared from the same plant species (i.e. *Camellia sinensis*) that includes the common names green tea, oolong tea, black tea, and white tea. An assortment of aqueous extractions similar to “tea” are prepared by different cultures throughout the world from a variety of plant species, however, for technical purposes during this discussion those will be termed tisane or herbal infusion. Green tea is prepared by steaming freshly harvested leaves to prevent oxidation that will produce a dry, stable product. Oolong tea is prepared by allowing the leaves to partially oxidize while black tea is prepared by allowing the leaves to whither allowing the oxidation of polyphenols. Each of these different tea preparations can dramatically alter the chemical and physical properties (i.e. taste, chemical constituents) of tea. The steeping of green tea leaves in near boiling water releases a rich variety of catechins as well as caffeine and theanine. Catechins are water soluble polyphenolic substances that include epicatechin-3-gallate (ECG), epigallocatechin (EGC), epigallocatechin-3-gallate (EGCG), and epicatechin (EC) (Fig. 1) (Balentine et al., 1997). Other less prominent polyphenols in green tea are quercetin, myricitrin and kaempferol. The most abundant polyphenol in green tea is EGCG accounting for 100 to 150 mg in a cup of brewed green tea and as such has been the focus of pre-clinical and clinical research in a variety of health settings.

Epidemiological studies of green tea for prostate cancer chemoprevention

Over the last two decades a host of epidemiological studies that include cohort and case-control studies have suggested that green tea consumption correlates with a lower risk of certain cancers that include breast, colon, and prostate. A collection of six epidemiological studies that included two case-control studies as well as four cohort studies evaluated the role of green tea in reducing the risk of developing prostate cancer and are briefly discussed below as well as summarized in Table 1 (Severson et al., 1989;Allen et al., 2004;Jian et al., 2004;Sonoda et al., 2004;Kikuchi et al., 2006;Kurahashi et al., 2008). In the majority of these studies a significant decrease in the development of prostate cancer was observed with increasing intake of green tea. Two studies that are often cited in reviews of green tea were also included in Table 1, however, it is important to point out that the type of tea was not defined and may or may not have included other teas (e.g. black, oolong, etc) or tisanes/herbal infusions (Villeneuve et al., 1999;Ellison, 2000). Not surprisingly, as with many epidemiological studies there are some conflicting reports about the role of green tea in cancer prevention. A case-control (1:2) study of 130 cases

of histologically confirmed adenocarcinoma of the prostate was carried out in southeast China and found that subjects who consumed 3 cups of green tea had a lower risk of developing prostate cancer [OR 0.27; 95% CI = 0.15–0.48] (Jian et al., 2004). Recently, a large cohort study of 49,920 subjects in Japan found that drinking >5 cups of green tea per day when compared to less than 1 cup per day showed a reduced risk of developing advanced prostate cancer [R 0.52; 95% CI 0.28–0.96] (Kurahashi et al., 2008). Three other cohort studies have been performed and found green tea had a non-statistically significant effect in decreasing the risk of prostate cancer (Allen et al., 2004;Kikuchi et al., 2006;Kurahashi et al., 2008). A fourth cohort study of Japanese ancestry subjects [n=7,999] from Hawaii (USA) prospectively analyzed the demographics and diet for the risk of developing prostate cancer and found a non-significant RR of 1.47 [95% 0.99 – 2.19] of developing prostate cancer with increased green tea consumption (Severson et al., 1989). Interestingly, this study also found an increased risk in subjects who consumed on a regular basis two other dietary constituents thought to have anti-cancer properties, soy and tofu.

Preclinical evidence of green tea constituents for prostate cancer chemoprevention

EGCG induces Apoptosis and Cell Cycle arrest

EGCG is the most abundant and most studied catechin and has significant growth inhibitory properties in prostate cancer cells with an observed IC_{50} from 40 μM to 80 μM. This inhibition is dependent on the length of exposure (i.e. 24 to 72 hours) as well as the cell line that was used (i.e. LNCap, DU-145, CWR22R*v*1, and PC3) (Ahmad et al., 1997; Kweon et al., 2006; Ravindranath et al., 2006). More importantly when a primary cell line such as normal epithelial cells are treated with EGCG there is no observable toxicity at doses that are used for cancer inhibition studies (Ahmad et al., 1997; Albrecht et al., 2008). A collection of reviews have commented on the possible mechanistic effects of EGCG in multiple cell lines and have primarily noted a similar collection of effects in regard to growth inhibition and cell cycle arrest (Adhami et al., 2004; Sarkar and Li, 2004; Khan et al., 2006).

The mitochondria is the central regulator of the intrinsic pathway of apoptosis and that is accompanied by the release of procaspases, cytochrome c, apoptotic protease-activating factor 1 (Apaf-1), endonuclease G and apoptosis-inducing factor (Green, 2000). In LNCap and DU145 prostate cancer cells EGCG was found to promote apoptosis as evidenced by DNA fragmentation at 40 μg/ml (i.e. 87 μM) and 80 μg/ml (175 μM) (Gupta et al., 2000). Confocal microscopy as well as flow cytometric analysis found a linear dose relationship of EGCG treatment (22 μM, 44 μM, 87 μM, and 174 μM) in the androgen insensitive DU145 cells

Using both LNCaP and DU145 cells a linear dose relationship between EGCG and apoptosis was observed by confocal microscopy and flow cytometry where apoptosis was found to be 9–53% and 14–58% respectively. A dose dependent cleavage of pro-caspase-3, -8, -9 was observed at 40 and 80 μM after 24 hours (Hastak et al., 2003). EGCG also had an effect on the transcription factors p53 and NF-κB that led to a change in the ratio of Bax/Bcl-2 in a manner that favors apoptosis. Other green tea catechins have been evaluated for inducing apoptosis resulting in a dose dependent effect in inducing apoptosis (i.e. ECG > EGCG > EGC > EC) (Chung et al., 2001). Additional studies have shown that EGCG induced G0/G1 phase cell cycle arrest in both androgen sensitive and androgen insensitive PCa cell lines in a dose dependent manner. Taken together these results suggest that regardless of androgen sensitivity and p53 tumor suppressor status green tea constituents decrease the growth of PCa *in vitro*.

EGCG acts as a sensitizing agent in LNCaP cells that are resistant to TRAIL induced apoptosis

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L) is a part of the extrinsic pathway of apoptosis and this death receptor pathway is often resistant in the androgen sensitive LNCaP cells (Mitterberger et al., 2007; Sanlioglu et al., 2007). Recently, a synergistic effect of EGCG (20 μM) when used in combination with TRAIL (100 ng/ml) was observed and resulted in three events: upregulation of poly(ADP-ribose) polymerase cleavage and modulation of pro- and anti-apoptotic Bcl-2 family of proteins, modulation of TRAIL R1 and Fas-associated death domain and FLICE-inhibitory protein proteins leading to decreased invasion and migration of LNCaP cells (Siddiqui et al., 2008a). Further evaluation of EGCG in combination with TRAIL revealed decreased invasion and migration as seen through inhibition of VEGF, uPA, angiopoieetin 1 and 2, MMP2,-3, -9 and upregulation of TIMP-1.

EGCG targets inflammatory pathways (NF-κB and COX-2)

Nuclear factor-kappa B (Nf-κB) is a redox sensitive transcription factor that is often overexpressed and has been suggested to regulate a variety of cellular activities that include inflammation, immune response, growth, and cell death. NF-kB resides in the cytoplasm bound to IkB rendering it inactive, however, once IkB is released NF-kB is translocated to the nucleus. EGCG has been shown *in vitro* to decrease the DNA binding activity of NF-κB and reduce the expression of the p65 subunit of NF-κB in LNCaP cells stimulated by TNFα (Hastak et al., 2003). The transgenic adenocarcinoma of the mouse prostate (TRAMP) model was developed to mimic the development of PCa from the precancerous prostatic interepithelial neoplasia to metastatic PCa and has served as a popular model for evaluating potential PCa chemoprevention and chemotherapeutic agents. When TRAMP mice are supplemented with a 95% enriched mixture of green tea polyphenols (GTP) in their drinking water as 0.1% w/v GTP a reduction in the expression of NF-κB and other relation proteins (IKKα, IKKβ, RANK, NIK) was observed compared to control mice (Gupta et al., 2000; Siddiqui et al., 2008b). These results are significant because NF-kB overexpression has been suggested to be an important target due to the regulation of a variety of down stream targets that include the cylcooxygenase-2 proteins

Another pro-inflammatory pathway that EGCG has been shown to target is Cyclooxygenase-2 (COX-2). Research has observed COX-2 overexpressed in PCa and this maybe secondary to over expression of NF-kB (Aparicio Gallego et al., 2007). In the androgen-dependent LNCaP prostate cells and androgen independent PC-3 prostate cells EGCG (10–100 μM) was shown to inhibit mitogen stimulated COX-2 expression (Hussain et al., 2005). *In vivo* studies also confirmed that green tea polyphenols reduced COX-2 expression (24%) as well as iNOS expression (77%) in the TRAMP model (Harper et al., 2007). The mechanism of EGCG-induced COX-2 inhibition appears to be through the regulation of transcription factors (e.g. NF-kB) as compared to the protein binding/inhibition of selective COX-2 inhibitors (rofecoxib, valdecoxib, celecoxib) (Smith et al., 2000).

EGCG targets MAP kinases (P38/JNK/ERK), PI3K-Akt, and PKC

MAPKs are serine threonine kinases that have been observed in various malignant cell lines to be involved in regulating cell proliferation and cell death. Six distinct groups of MAPKs are known that include extracellular signal-regulated kinases (ERK1 and ERK2), c-Jun N-terminal kinases (JNKs), p38 isoforms, ERK5, ERK3/4, ERK3 and ERK 7/8 (Albrecht et al., 2008). Modulation of ERK1/2 and p38 was observed in DU-145 cells with effects seen at 10 to 20 μM of EGCG (Vayalil and Katiyar, 2004). *In vivo* evaluation in TRAMP mice found that GTP (0.1%) in drinking water reduced the phosphorylation of ERK1/2 by 50–62% in the dorsolateral prostate ($p<0.01$) (Vayalil and Katiyar, 2004). In another study, EGCG (0.06%) alone in drinking water led to a reduced expression of ERK1 and 2 phosphorylation by 57 and 45%

respectively in the ventral prostate compared to a 92 and 93% reduction respectively in the dorsolateral prostate (Harper et al., 2007).

PI3k/Akt plays an important role in a variety of signaling pathways that can regulate cell growth, survival and motility. Green tea polyphenols decreased PI3K and Akt expression in LNCap and DU-145 cells (Siddiqui et al., 2004). This mechanism of cancer inhibition was reproducible in the TRAMP mouse model where GTP was shown to reduce PI3K levels by 67–79% ($p<0.01$) and also reduced the phosphorylation of AKT (Thr308) by up to 65% ($p<0.01$) (Adhami et al., 2004).

EGCG targets the insulin-like growth factor axis

The IGF (insulin-like growth factor) axis has been suggested to regulate the growth and development of a variety of cancers, including prostate cancer. IGF-1 is the ligand for IGF-1 receptor, a tyrosine kinase that regulates the MAPK and PI3k/Akt signaling pathways. IGF ligands in the plasma are complexed to IGFBPs (insulin-like growth factor binding proteins) that function to transport IGFs and modulate their activity. IGFBP-3 has been shown to be a substrate for PSA and it has been suggested that as PSA levels rise during the natural progression of PCa and proteolytically cleave IGFBP-3 thereby increasing the bioavailable IGF at the cellular level (Kaplan et al., 1999). Epidemiological studies have evaluated serum IGF levels and found that as serum IGF levels are increased there is an increased risk of PCa. TRAMP mice when administered a combination of green tea polyphenols (0.1%) in drinking water were observed to alter the serum IGF-1 and IGFBP-3 ratio by 70 to 83% ($p<0.01$) (Adhami et al., 2004) Alteration of IGF-1 by GTP was further confirmed by immunohistochemical analysis of the dorsolateral prostate with decreased IGF-1 seen after 16, 24 and 32 weeks of ingestion compared to controls. Further *in vitro* evaluation has shown that EGCG inhibits IGF-1 receptor activity with an IC_{50} of 14 μm (Li et al., 2007). In addition to direct inhibition of IGF-1 receptor EGCG (0.6%) decreased IGF-1 and IGF-1 receptor protein levels in the ventral prostate of TRAMP mice (Harper et al., 2007).

EGCG targets the androgen receptor and decreases PSA

The androgen receptor is a nuclear receptor that is activated by the binding of hormones such as testosterone and 5α-dihydrotestosterone and has been aggressively pursued as an intervention target in preventing or treating PCa. Briefly, the androgen receptor is found in the cytoplasm where it is complexed to heat shock proteins rendering it inactive until a ligand such as 5α-dihydrotestosterone binds it. The androgen receptor is then translocated to the nucleus where it dimerizes and can act as a DNA transcription factor for up to 1,532 genes such as prostate specific antigen (PSA). EGCG and green tea extract were shown to reduce gene expression and protein expression of AR in the androgen dependent LNCaP cell line at concentrations of 10–20 μM (Ren et al., 2000). Supporting these observations was *in vivo data* in athymic nude mice implanted with CWR22Rv1 cells administered green tea polyphenols (0.1%) in drinking water that resulted in a reduced tumor volume and serum PSA levels (control group PSA (ng/mL) of 13.95 ± 0.82 ng/ml, treatment group PSA of 4.95 ± 1.23 ng/ml) as compared to controls (Siddiqui et al., 2006). Using PSA decrease as evidence of GTP effects on AR or other prostate signaling pathways is tempered by *in vitro* evidence suggesting that EGCG decreases the transcription and translation of PSA (Siddiqui et al., 2006). In addition to careful interpretation of GTP effects due to multiple possible mechanistic actions, recent evidence suggests disparate regional effects within the prostate. EGCG (0.6%) provided in drinking water to 12 week old TRAMP mice resulted in decreased AR protein expression in the ventral prostate (VP) (41%, $p<0.001$) and increased expression in the dorsolateral prostate (DLP) (121%) when compared to control (Harper et al., 2007).

Another important target of androgen signaling, relative to prostate carcinogenesis is 5 α-reductase that is responsible for the conversion of testosterone to dihydrotestosterone (DHT). There are two isozymes of 5α-reductase (Type 1 and Type 2), that are encoded by separate genes and have different biochemical and pharmacological properties. In addition, this enzyme is expressed at different levels in prostate tissue (i.e. primarily type 2) vs. non-prostate tissue (i.e. primarily type 1) (Andersson and Russell, 1990). Both testosterone and DHT are ligands for the androgen receptor, however, DHT has a 4–5 fold higher affinity when compared to testosterone. In a cell free biochemical based assay ECG and EGCG were found to inhibit the type I human isozyme with an IC_{50} of 12 μM and 15 μM, respectively, however, these effects were not observed in a whole cell based assay (Liao and Hiipakka, 1995). Structure activity relationship studies of the green tea catechins have suggested that the gallyl or galloyl group may interact with a specific site on 5α-reductase (Hiipakka et al., 2002).

EGCG targets detoxification enzymes

Xenobiotics that include drugs and carcinogens are primarily eliminated through metabolic pathways that include phase I biotransformation enzymes (oxidation and reduction) and phase II conjugation enzymes. The cytochrome P450 monooxygenase family (CYP1, CYP2, and CYP3) are responsible for phase I metabolism and promote oxidation, hydroxylation, reduction, and hydrolysis. Phase II reactions conjugate xenobiotics with an ionic hydrophilic moiety by UDP-glucuronosyltransferases, glutathione *S*-transferases (GST), sulfotransferases, and *N*-acetyltransferases (NAT) to increase water solubility, decrease lipid solubility and promote urinary elimination of xenobiotics. Glutathione S-transferase has three distinct classes, α, μ, and π are expressed in hepatic and extrahepatic tissues. GST-π is the most abundant isozyme and is expressed in blood lymphocytes, colon, rectum and the prostate.

A clinical investigation in 42 healthy participants evaluated the repeated administration of green tea as Polyphenon E to assess the affect on Phase I and Phase II detoxification enzymes in humans (Chow et al., 2007). The major GST isozyme, GST-π, was increased from 2,252.9 ± 734.2 to 2,634.4 ± 1,138.3 ng/mg protein, ($P = 0.035$) in blood lympocytes and was only significant in patients who were in the lowest tertile of baseline level with a mean increase of 80%. A subset analysis of patients stratified by baseline GST activity suggests that subjects with the lowest baseline GST activity had the most benefit from Polyphenon E. A possible effect upon GST-π could be significant because the silencing of GST-π occurs in the vast majority of high grade prostatic intraepithelial neoplasia (PIN) and prostate carcinomas due to aberrant methylation in the 5-promoter region (Meiers et al., 2007).

Green Tea Catechins inhibit the DNA replication protein MCM7 in PCa

MCM7 is an essential component for DNA replication and is a part of the replication helicase complex (MCM2-7) where DNA is expressed during late M to early G1 phases of the cell cycle (Lei, 2005). Aberrant expression of MCM proteins have been reported in a variety of cancers, however, only MCM7 is highly expressed in prostate cancer. In another study using TRAMP mice using gene expression profiling with a GeneChip Mouse Genome 430 2.0 arrays (Affymetrix, Santa Clara, CA) found that MCM7 is overexpressd in TRAMP mice by as much as 11-fold at 24 weeks (McCarthy et al., 2007). When TRAMP mice were administered green tea catechins (0.3%) in drinking water a significant ($p<0.001$) decrease in MCM7 protein expression was observed compared to their counterparts consuming water. This protein represents a unique target of green tea catechins that is associated with the progression, growth, and tumor invasion within the prostrate.

Pharmacokinetics of green tea catechins

Absorption

Preclinical pharmacokinetic studies of green tea have consistently shown that green tea catechins have low oral bioavailability in rodents with estimates ranging from 2% to 13% (Zhu et al., 2000). Oral bioavailability in humans can not be estimated due to the lack of an available IV formulation. Multiple processes could contribute to the low bioavailability of tea catechins that include low solubility in the gastrointestinal fluid, poor membrane permeability, degradation/metabolism in the gastrointestinal tract, transporter-mediated intestinal secretion/efflux, and presystemic hepatic elimination. Green tea catechins have been shown to be quite stable at a pH <6.5, however, EGC and EGCG are rapidly degraded at a pH >7.4 (Yoshino et al., 1999). Tea catechins would be expected to be rather stable in the stomach, however, once EGC and EGCG enter the gastrointestinal tract (pH range of 5–8) they will be more susceptible to degradation possibly explaining the low bioavailability of tea catechins. Interestingly, EC has been found to be stable at a pH range of 1.8 to 11.2.

Several pharmacokinetic studies have been performed using a standardized pharmaceutical grade preparation of green tea polyphenols known as Polyphenon E (200 mg of EGCG, 37 mg of EGC, 31 mg of EC per capsule) and has been used in single dose, multiple dose, and various dosing conditions in healthy volunteers(Chow et al., 2001; Chow et al., 2003; Chow et al., 2005). Polyphenon E (Mitsui Norin, Ltd) was granted an investigational new drug (IND) status in the United States by the FDA with each capsule containing 80 to 98% total catechins by weight standardized to EGCG that comprises 50 to 75% of the substance. The remainder of the material is comprised by other catechins that include epicatechin, epigallocatechin, and epicatechin gallate. As a point of interest Polyphenon E is essentially decaffeinated with caffeine only comprising ~0.5% w/w. In a single dose phase I pharmacokinetic study a combination of green tea catechins (EGCG, EGC, EC, and other tea polyphenols) was compared to pure EGCG for differences in pharmacokinetic parameters (Chow et al., 2001). Briefly, patients fasted after midnight and were allowed to have one or two bagels for breakfast and were administered study drug capsules of Polyphenon E or pure EGCG and were randomized to receive either 200 mg, 400 mg, 600 mg or 800 mg of EGCG with the two different formulations. The pharmacokinetic parameters AUC, C_{max}, T_{max}, CL/F, V/F, and $T_{1/2}$ of EGCG were found to be equivalent between the two formulations. After Polyphenon E administration the average EGCG plasma C_{max} (ng/ml) was 72.7 ± 66.4, 125.3 ± 50.4, 165.7 ± 126.9, and 377.6 ± 149.8 ng/ml at the four dose levels. These results suggest that the other green tea catechins do not have any effect on the pharmacokinetics of EGCG.

A second pharmacokinetic study evaluated the role of a fasted or fed state on the pharmacokinetic parameters of Polyphenon E (400, 800, or 1200 mg of EGCG) in thirty healthy volunteers (Chow et al., 2005). Plasma levels of EGCG and ECG were primarily in the free form while EC and EGC were present in the glucuronidated or sulfate conjugate forms. In the fasting condition 800 mg of EGCG had a >5 fold higher average maximum plasma concentration (C_{max}) of free EGCG compared to the fed condition, 1522.4 ± 1357.8 (ng/ml) and 294.0 ± 113.5 (ng/ml) respectively. The C_{max} levels of free catechins (EGCG, EGC, and EC) were found to be dose dependent and higher in the fasted state compared to the fed state.

Distribution

Tissue levels of green tea catechins were estimated in male Sprague Dawley rats (300 grams) that had *ad libitum* access to 0.6% green tea polyphenols in their drinking water for 14 days (Kim et al., 2000). The highest concentration of EGCG was found in the large intestine (487.8 +/− 121.5 ng/g) whereas the highest concentration of EGC was in the bladder (810.4 +/− 299.4) that approximates to 1.1 μM EGCG and 2.6 μM EGC. Other tissues of significant EGCG and

EGC concentrations included the kidney, prostate, and lung. Prostate tissue that was examined contained EGC (250.6 ± 66.1), EC (234.5 ± 59.2), and EGCG (57.7 ± 20.9) that calculates to 0.8 μM, 0.8 μM and 0.1 μM respectively. Low concentrations of tea catechins were observed in the liver, spleen, heart, and thyroid.

In a human study twenty participants were randomized to consume 236 ml five times daily (1.18 l) of green tea, black tea, or soda five times daily as a control for five days before radical prostatectomy and prostate tissue was analyzed for concentration of various tea catechins (Henning et al., 2006). Each cup of green tea was 236 ml and contained 90.6 mg of EGC, 25.5 mg of EC, 71.2 mg of EGCG, and 39.8 mg of ECG in addition to other flavanoids to bring the total flavanol concentration to 227 mg per cup of green tea. After 5 days of continuous green tea intake prostate samples tissues were found to contain EGC (100 pmol/g), EC (43 pmol/g), EGCG (40 pmol/g) and ECG (21 pmol/g).

Metabolism and Elimination

Presystemic hepatic metabolism is often an explanation for the low bioavailability of drugs and represents a potential pitfall in the successful development of new chemical entities. To understand the possible role of the first pass effect EGC, EC, and ECG were infused directly into the portal vein of rats and plasma concentration of tea catechins measured suggested minimal first pass hepatic elimination (Cai et al., 2002). Another possible mechanism of eliminating green tea catechins is by transporter mediated intestinal efflux and has been evaluated using the Caco-2 cell line (Vaidyanathan and Walle, 2001; Zhang et al., 2004; Zhang et al., 2006). A 50% decrease in the efflux of EC was observed in the Caco-2 model once MK-571, a competitive inhibitor of the MRP2 transporter was co-administered with EC (Vaidyanathan and Walle, 2001). There is some evidence to suggest that non-gallate catechins are more susceptible to efflux compared to gallate catechins (Zhang et al., 2004). The degree of efflux transport of green tea catechins in descending order was EC > EGC > ECG and EGCG.

The gastrointestinal tract represents a complex environment of intestinal flora and enzymes that are able to modify and help remove foreign compounds. In a Phase I pharmacokinetic study patients were administered Polyphenon E and serum samples were analyzed for glucuronic acid and sulfate conjugates. Enzymatic treatment of human plasma samples found that EGCG is minimally conjugated to glucuronate or sulfate, however, EGC and EC were found to be extensively glucuronidated or sulfated (Chow et al., 2001). Piperine is a known reversible inhibitor of UDP-glucose dehydrogenase (UDP-GDH) that has been used to increase the bioavailability of curcumin and has also been shown to increase the bioavailability of EGCG (Lambert et al., 2004; Johnson and Mukhtar, 2007).

When Polyphenon E was administered on an empty stomach after an overnight fast there was a remarkable increase in the blood levels of free EGCG, EGC, and ECG when compared to subjects who took polyphenon E with food (Chow et al., 2005). One possible explanation of this is that food is known to delay gastric emptying as well as raise the pH of the stomach thereby decreasing the stability of green tea catechins. In addition, food is known to have reversible or irreversible effects in the small intestine, modulate the dissolution rate of a drug, and release bile acids that may interact with drugs.

Safety and toxicity of green tea and EGCG

To our knowledge there are very limited reports of adverse reactions with green tea consumption in light of the fact that some cultures consume greater than 10 cups of green tea per day. The most notable side effect to date in clinical trials that has been observed were reports of “jitteriness” that has been suggested to be a result of caffeine intake (Pisters et al., 2001). Pharmaceutical grade preparations that are being used in investigational settings such

as Polyphenon E have a very limited amount of caffeine (~0.5% w/w) and could be considered caffeine-free. Green tea dietary supplements have the potential to significantly increase the amount of green tea catechins that are consumed on a daily basis when compared to ingesting tea as a beverage and have been reported in multiple case reports as inducing liver toxicity (Gloro et al., 2005; Molinari et al., 2006). The cytotoxicity of green tea extract on rat hepatocytes was inconclusive in showing that EGCG (100–500 μg/ml medium) has a toxic effect. This was regardless of the fact that the concentrations used were significantly greater (i.e. >100×) than what is observed in human serum after green tea consumption (Schmidt et al., 2005). If green tea catechins are not responsible for the hepatotoxicity one possible explanation may be that a component of the extract or contamination during the growing process or production of the extract is the culprit.

A series of publications evaluated the product Teavigo®, an EGCG rich product (≥88.1 – 95% pure), using FDA guidelines to prepare novel pharmaceuticals for investigational new drug status. Genotoxic studies that included Ames test, ML/TK assay, and an *in vivo* micronucleus tests revealed that Teavigo was not genotoxic even when administered to animals at much higher doses that what would be used in humans (Isbrucker et al., 2006a). A second series of short term toxicity studies evaluated with the product Teavigo found the NOAEL (no observable adverse effect level) of EGCG was 500 mg/kg when administered to rats for 13 weeks (Isbrucker et al., 2006a). Animal toxicology studies designed according to an FDA guidance for developmental toxicology studies evaluated the teratogenecity and reproductive toxicity of EGCG in Wistar rats (Isbrucker et al., 2006b). Further analysis of a two- generation study in rats fed 1200, 3600, and 12,000 ppm had no adverse effects on reproduction or fertility. In summary, these three publications suggest that doses of 200mg/kg/day of EGCG in animals is the NOAEL (no-observed adverse effect level).

The safety of multiple doses of EGCG and Polyphenon E was assessed in 40 healthy participants over a 4 week period and were monitored for adverse events as well as systemic exposure to green tea catechins (Chow et al., 2003). Participants were randomized to receive 800 mg EGCG once/day, 400 mg EGCG, 800 mg EGCG as Polyphenon E once/day or 400 mg of EGCG as Polyphenon E once per day and were monitored for adverse events as well as pharmacokinetic parameters. Patients who received 400 mg of Polyphenon E had a C_{max} (ng/ml) of 179.9 ± 114.3 after the first dose and after four weeks of daily dosing patients had a 155.4 ± 61.9. Patients who received 800 mg of EGCG as Polyphenon E had a C_{max} of 263.8 ± 135.7 after day 1 and a level of 287.6 ± 124.2 at the end of the 4 week study. Based on the results of multiple dosing of EGCG in two different formulations it is not expected to accumulate in the body. The most often cited adverse event was mild and transient nausea and was observed at the highest dose used (1200 mg EGCG) when patients were fasting and is leading investigators to design studies of 800 mg of EGCG per day.

The potential of clinically relevant drug interactions with green tea catechins was assessed by combining isozyme specific metabolic probe drugs with Polyphenon E (Chow et al., 2006). The P450 enzyme system is responsible for metabolizing clinically important drugs and are listed in descending order, CYP3A4 (36%), CYP2D6 (21%), CYP2C9 (17%), and CYP1A2 (8%) (Rendic and Di Carlo, 1997).Four weeks of continuous Polyphenon E consumption did not alter the activity of CYP1A2, CYP2D6, and CYP2C9 and only showed a 20% increase ($p=0.01$) in the AUC of plasma buspirone (CYP3A4) implying slight inhibition of CYP3A4 did occur, however, the authors concluded that continuous green tea catechin consumption would not result in clinically significant effects on drug metabolizing enzymes. These results were consistent with a smaller clinical trial (n=11) that found green tea did not alter CYP2D6 or CYP3A4 activity (Donovan et al., 2004).

Clinical trials of green tea for the prevention and/or treatment of prostate cancer

At present there are three published clinical trials using different forms of green tea preparations for the prevention (n=1) or treatment (n=2) of prostate cancer. Two of these studies were performed in late stage hormone refractory PCa while another study was performed in patients who were identified as having prostatic intraepithelial neoplasia (PIN), a pre-cancerous lesion of the prostate and are summarized below.

Trial 1 – An open label Phase II trial in biopsy proven malignant hormone refractory prostate cancer

A multi-institutional single arm open label Phase II trial evaluated the effect of green tea powder in 42 patients who had biopsy proven hormone refractory prostate carcinoma (Jatoi et al., 2003). The green tea powder consisted of pulverized green tea mixed with sugar, citric acid, and flavoring. Patients took 1-gram of green tea powder in warm or cold water six times per day. Each dose of green tea powder contained 100 calories and 46 mg of caffeine. Among the 42 eligible patients one patient had a 50% decrease in PSA from baseline (229 ng/dl to 105 ng/dl), however, this effect was not sustained beyond 2 months. This suggests that overall there was a 2% response rate and was below what was expected to happen by chance alone. After one month the median change in PSA from baseline was a 43% increase. While the study observed little to no therapeutic activity, the results need to be interpreted in the context of the study population (advanced state prostate carcinoma with multiple prior therapies), the trial design (open label trial not designed to detect small effects with administration for only one month), and the formulation used (a unique product with no information about concentration of green tea polyphenols).

Trial 2 – An open label clinical trial in hormone refractory prostate cancer

A second single arm open label trial evaluated the effect of a standardized green tea extract in nineteen patients who were diagnosed with hormone refractory prostate cancer (Choan et al., 2005). The median age of patients in this study was 76 years old and the median PSA was 161 ng/ml (8.5–588). Patients in this study were administered green tea extract capsules (Sabinsa Corp, Piscataway, NJ) at a dose of 250 mg twice daily. Each capsule contained 75% polyphenols of which greater than 30% was EGCG and caffeine was less than 2%. Fifteen patients completed a minimum of two months of therapy – nine patients had progressive disease within 2 months of starting therapy and six patients developed progressive disease after an additional 1 to 4 months of therapy. Due to the aforementioned study by Jatoi et al (see above) an unscheduled interim analysis of this study (Jatoi et al., 2003) noted a remote probability of a positive clinical outcome and subsequently halted the study. An issue with this study is the lower dosing of GTE. The dose of 500 mg/day (~150 mg EGCG) is significantly lower than what has been used in the pharmacokinetic studies with Polyphenon E (400 to 1200 mg EGCG) and may represent a dosing discrepancy of 2.6 to 8 fold less of daily EGCG. There were some possible hints of biological activity in that 6 of 19 patients briefly (1–4 months) had stabilization of their PSA regardless of the lower dose of EGCG. Similar to the aforementioned study, this study also examined advanced disease patients with extensive prior treatment and employed a formulation not easily duplicated. In summary, this study provides some valuable insights into green tea and its use in late stage prostate cancer and may suggest that hormone refractory PCa patients are not an ideal population, however, significant questions still exist.

Trial 3 – A proof of principle clinical trial of green tea for the chemoprevention of PCa

In 2006 a randomized, double blind, placebo controlled trial of 60 patients was performed as a proof-of- principle clinical trial to assess the safety and efficacy of GTCs for the

chemoprevention of PCa in HG-PIN volunteers is shown in Fig. 1 (Bettuzzi et al., 2006). Patients were randomized to 600 mg GTCs per day (i.e. three 200 mg capsules) with each capsule containing [EGC (5.5%), EC (12.2%), EGCG (51.9%), ECG (6.1%), total GTCs, (75.7%), and caffeine (<1%)]. The subjects were patients recently diagnosed with HG-PIN, which based on historical studies have a 30% likelihood of developing PCa at one year. As expected 9/30 patients (i.e. 30%) receiving placebo developed PCa after one year while only 1 patient (i.e. 3%) randomized to GTC developed PCa. Total PSA was not noticeably different between the two arms, however, patients randomized to GTCs showed values lower than patients on placebo suggesting that PSA may not be an ideal biomarker for green tea catechin studies in this population. A secondary observation was patients with concurrent BPH randomized to GTCs showed improvement in the International Prostate Symptom Score (statistically significant) and quality of life scores. The most significant difference between this study and the clinical trials by Jaioti et al and Choan et al is patients enrolled in this study had a precancerous lesion as compared to metastatic prostate cancer. A two year follow up was performed in a subset of the participants and found that the effect of PCa prevention was long lasting with green tea catechins (Brausi et al., 2008). These results are encouraging and provide rationale for additional clinical trials evaluating the efficacy of green tea polyphenols as a cancer chemoprevention agent.

Trial 4 – Short term supplementation with standardized green tea polyphenols decrease serum biomarks in prostate cancer patients

A phase II open label, single arm two stage clinical trial to evaluate the effects of standardized green tea polyphenols during the interval between prostate biopsy and radical prostatectomy was recently completed (McLarty et al., 2009). Short term supplementation was performed with Polyphenon E (contained 800 mg of (−)-epigallocatechin-3-gallate (EGCG) and lesser amounts of (−)-epicatechin, (−)-epigallocatechin, and (−)-epicatechin-3-gallate (a total of 1.3 g of tea polyphenols), until time of radical prostatectomy (i.e. median dosing period 34.5 days). Several biomarkers were evaluated during the clinical trial that included HGF, VEGF, PSA, IGF-1, IGFBP-3, and IGF-1/IGFBP-3 ratio. A significant decrease was observed in serum levels of HGF, VEGF, PSA, IGF-I, and IGFBP-3 (all $p<0.03$, Wilcoxon signed rank test). The IGF-I/IGFBP-3 ratio also changed significantly. In addition, several reports have suggested that high doses of EGCG were found to be toxic, however, no effects on liver function were observed (total protein, albumin, bilirubin, conjugated bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, amylase, and lipase).

In should be noted the effect of Polyphenon E on serum levels of PSA was modest, however, this needs to be interpreted with caution. A variety of physiological paramaters unrelated to cancer progression can alter serum levels of PSA. In addition, PSA may not accurately reflect changes in cancer cell number or tumor size. These data support a potential role for standardized green tea polyphenols in prostate cancer chemoprevention.

Conclusions and future directions

Over the last 15 years an intensive effort that includes epidemiological, pre-clinical and early clinical investigations has been performed to evaluate the role of green tea in the prevention and/or treatment of prostate cancer (PCa). EGCG the main constituent of green tea has been shown in cell culture as well as animal models to down regulate pro-inflammatory pathways, multiple kinases, the insulin like growth factor axis, as well blunt the effects of androgens. In addition, animal models that include xenograft tumor models (Table 2) as well as transgenic animal studies (Table 3) have suggested that green tea polyphenols can decrease the tumorigenic potential of prostate cancer. Early human clinical investigations have shown when

a defined green tea product (e.g. Polyphenon E) is used the product is safe and tolerable. Even more encouraging is a prospective, double-blind, placebo-controlled study over 12 months using a defined product of green tea in capsule form in men with HG-PIN that observed a 90% reduction in developing PCa. The results of this trial has led to a larger clinical trial in the United States of 272 HG-PIN patients that began in 2007 and will evaluate the role of 200 mg EGCG as Polyphenon E twice daily (i.e. 400 mg EGCG/day) over a one year period with a primary endpoint of rate of progression to PCa. The selection of an at risk population (i.e. HG-PIN) in combination with a standardized green tea extract by Bettuzzi and colleagues has brought renewed interest to green tea for cancer chemoprevention. Clinical trials of green tea for PCa have largely focused on precancerous lesions (i.e. HG-PIN) or late stage hormone refractory PCa, however, there is a significant gap in the knowledge available for patients that are classified as having localized PCa. This group of patients may represent an ideal population given that they often undergo watchful waiting without any pharmaceutical interventions as well as the fact that PSA is a routinely used biomarker. More recently, short term supplementation with green tea polyphenols in patients undergoing radical prostatectomy was found to decrease serum biomarkers associated with prostate cancer.

What has become evident over time is the necessity to use standardized green tea polyphenols for interventional purposes as opposed to a green tea infusion. This is an important point to illustrate being that with a green tea infusion there is no assurance of the contents of the infusion being that environment, cultivation, and brewing technique can influence the content of a green tea infusion. This point could not be further illustrated in the example of a previous clinical trial that evaluated an unstandardized green tea infusion in metastatic prostate cancer patients. Regrettably, the results of this study halted a second study where several patients receiving what is now considered a low dose of green tea extract showed a delay in the elevation of PSA in several patients. As mentioned earlier a recent clinical trial has now been performed using a standardized green tea extract (e.g. Polyphenon E) in patients undergoing radical prostatectomy a decrease in prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients is observed (McLarty et al., 2009). It is imperative that future studies that are evaluating plant based materials be well characterized before clinical trials are performed. The evidence that has been collected by multiple investigators suggests that green tea may be a promising agent for PCa chemoprevention and further clinical trials of participants at risk of PCa or early stage PCa are warranted.

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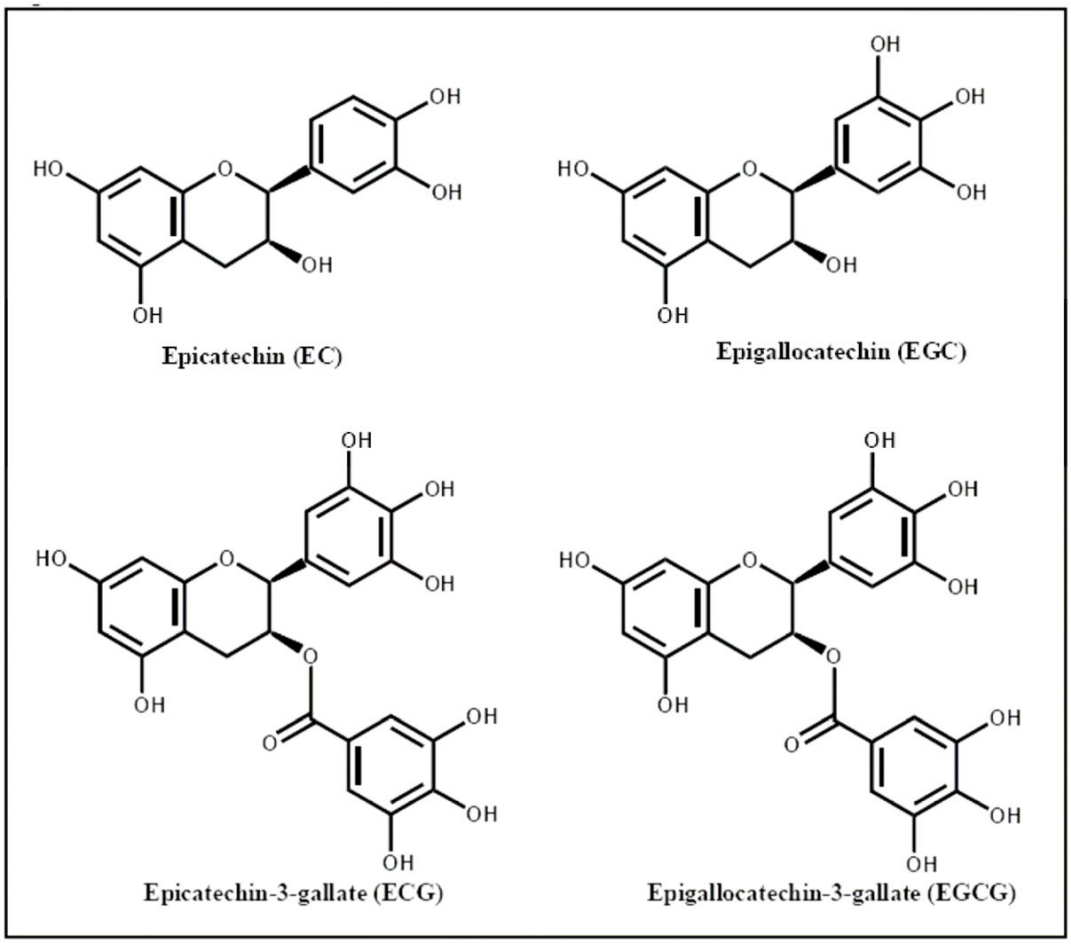

Fig. 1. Green tea Polyphenols

A variety of constituents are released during the brewing process of green tea (*Camellia sinensis*) that include polyphenols known as green tea catechins. These catechins include epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin-3-gallate.

Table 1

Summary of epidemiological studies that evaluated green tea (*Camellia sinensis*) for prostate cancer prevention.

Type of Tea	Location	Design [*n*] [Duration]	Tea Intake	RISK (OR/RR/HR)	Year
(Kurahashi et al., 2008)					
Green	Japan	Cohort [50,436] [1990–2004]	<1 cup/day 1–2 cups/day 3–4 cups/day ≥5 cups/day Total	1.0 [a] 1.12 (0.65–1.94) 0.86 (0.5–1.47) 0.60 (0.34–1.06) p = 0.03* 0.52 (0.28–0.96) p = 0.01*	2008
(Kikuchi et al., 2006)					
Green	Japan	Cohort [26,481] [1994–2001]	<1 cup/day 1–2 cups/day 3–4 cups/day ≥5 cups/day	1.0[b] 0.77 (0.44–1.43) 1.15 (0.69–1.94) 0.85 (0.50–1.43) p = 0.81*	2006
(Sonoda et al., 2004)					
Green	Japan	Case-control [140 (1:1)] [2000–2002]	<1 cup/day 1–2 cups/day 3–4 cups/day ≥5 cups/day	1.0[c] 0.99 (0.48–2.03) 0.79 (0.38–1.63) 0.27 (0.27–1.64) p = 0.30*	2004
(Allen et al., 2004)					
Green	Japan	Cohort [~ 93,000] [1958–1978]	<1 cup/day 2–4 cups/day ≥5 cups/day	1.0[d] 1.03 (0.69–1.55) 1.29 (0.84–1.98) p = 0.16*	2004
(Jian et al., 2004)					
Green	SE China	Case-control [130 (1:2)] [2001–2002]	<1 cup/day 1–3 cups/day >3 cups/day	1.0[e] 0.53 (0.30–0.94) 0.27 (0.15–0.48)	2004 †
(Severson et al., 1989)					
Green	Hawaii ‡	Cohort [7,821] [1965–1986]	never ever	1.0[f] 1.47 (0.99–2.19)	1989
(Ellison, 2000)					
Undefined	Canada	Cohort [1970–1993]	0 >0–250 mls >250–500 mls >500–750 mls >750 Any	1.0[g] 1.22 (0.72–2.08) 1.27 (0.75–2.16) 1.00 (0.58–1.73) 1.03 (0.58–1.82) 1.13 (0.72–1.76)	2000
(Villeneuve et al., 1999)					
Undefined	Canada	Case-control [1,623 (1:1)] [1994–1997]	0 <1 cup 1–3 cups/day ≥4 cups/day	1.0[h] 0.9 (0.8–1.2) 1.0 (0.9–1.5) 1.1 (0.8–1.5) p = 0.11*	1999

[a] RR adjusted for all possible confounders;

[b] HR adjusted for age, BMI, alcohol consumption, smoking status, marital status, calorie intake, calcium intake, walking duration, consumption frequencies of black tea, coffee, meat, and fish;

[c] OR adjusted for cigarette smoking and energy intake;

[d] RR adjusted for age, calendar period, city of residence, radiation dose, and education level;

[e] adjusted OR;

[f] RR;

[g] RR adjusted for five year age group;

[h] OR adjusted by age, province of residence, race, years since quitting smoking, cigarette pack years, BMI, rice and pasta, coffee, grains and cereals, alcohol, fruit juices, tofu, meat, income and family history of cancer;

[†] Jian takes into account tea preparation tea leaves kg/year, g/batch, cups/day)

[‡] Japanese ancestry;

[*] p-value for trend;

Abbreviations: OR = odds ratio; HR = hazard ratio; RR = relative risk; SE = southeast; BMI = body mass index.

Table 2

Summary of green tea interventions using non-transgenic mice inoculated with prostate cancer cells.

Mice	Formulation	Cell line	Route of Delivery	Results	Year
(Siddiqui et al., 2006)					
nu/nu	EGCG (62%) ECG (24%) EGC (5%) EC (6%)	CWR22Rv1[a]	oral, 0.1% GTP[e] as drinking water	Protocol 1 (chemoprevention): GTP delayed tumor reaching 1200 mm^3 by 28 days [i] GTP decreased PSA at day 18 from 13.95 to 4.95 ng/ml [j**] GTP decreased PSA at day 24 from 26.4 to 4.46 ng/ml [j**]	2006
			0.05% and 0.01% GTP[e] as drinking water	Protocol 2 (chemotherapy): GTP delayed tumor reaching 1200 mm^3 by 5 days (0.01% GTP) And 12 days (0.05% GTP) [k]	
(Zhou et al., 2003)					
SCID	Total catechins (3893.9 uM) EGCG (1780.5 uM) ECG (448.7 uM) EGC (1152.7 uM) EC (512.2 uM)	LNCap[b]	oral, 15 gms tea leaves[f]/liter as drinking water	GTI reduced tumor weight 22% (p = 0.11) GTI reduced tumorigenicity 44.6% * GTI reduced lymph node metastases by 7.1% * GTI did not alter food intake or final body weight *	2003
(Liao et al., 1995)					
BALB/c	Purified catechins (>98%)	PC3[c] and LNCap 104-R[c]	Injection, 1 mg EGCG[g] d 1–14	PC3 cell inoculation: 1 mg EGCG halted tumor growth/reduced tumor size in some cases by 20–30% if treated on day 1–14 (i.e. post tumor inoculation). 1 mg EGCG regressed tumors rapidly in the first 7 days 1 mg EGCG was started on day 28 the tumor regressed rapidly during days 28–35 but not significantly the following week. LNCap cell inoculation: 1 mg EGCG nearly abolished tumor in castrated mice.	1995
(Sartor et al., 2004)					
C57/B1	GTE EGCG (59%) 0.5% Caffeine	TRAMP C1[d]	oral, 0.6% GTE[h] as drinking water supplied 3 days prior to injection until end of study.	GTE had no effect compared to control mice on tumor size at day 33. GTE when given to mice co-inoculated with LPS and TRAMP-C1 reduced tumor size from 640 mm^3 to 200 mm^3 (p = 0.036) GTE did not cause reduced body weight	2004

[a] 1×10^6 cells implanted in left and right flank;

[b] 2×10^6 cells inoculated intraprostatically,

[c] 1×10^6 cells injected SC in one or both flanks,

[d] 1.3 × 106 cells injected SC, animals were euthanized at when control mice reachd 650 mm^3,

[e] Mitsui Norin Co. Ltd., Shizuoka, Japan,

[f] China Green Tea, Shanghai Tea Import and Export Corp.

[g] Funakoshi Co, Sigma Chemical Co., or purified by authors,

[h] SOFAR, Italy,

[i] protocol 1 (i.e. chemoprevention) began administration on day 1 of tumor implantation.

Control arm of the study reached a tumor volume of 1200 mm^3 in 26 days and treatment arm reached tumor volume of 1200 mm^3 in 54 days,

[j] percent decrease compared to control mice at day 18 and day 24 (i.e. 13.95 ng/ml and 26.4 ng/ml respectively),

[k] protocol 2 (i.e. chemotherapy) began GTP (0.01% and 0.05%) administration when tumor volume was 400 mm^3.

Control arm of the study reached tumor volume of 1200 mm^3 in 39 days and treatment arm reached tumor volume of 1200 mm^3 in 44 days (0.01% GTP) and 51 days (0.05%);

** $p = <0.01$,

* $p = <0.05$,

Abbreviations: GTP = green tea polyphenols; GTI = green tea infusion

Table 3

Summary of green tea interventions using the TRAMP (transgenic adenoma of the mouse prostate) mouse.

Mice	Formulation	Route of Delivery	Results	Year
(McCarthy et al., 2007)				
C57BL/6	EGC (5.5%), EC (12.2%)	GTC [b] (0.3%) in drinking water	GTC chemopreventive activity was evident in as many as 80% of the transgenic animals.	2007
	EGCG (51.9%), ECG (6.1%) Caffeine (<1%)		MCM7 expression level decreased starting at 12 wks of age with GTCs.	
(Harper et al., 2007)				
C57BL	EGCG (93%) extracted from non-fermented *Camellia sinensis*[a]	EGCG[a] (0.06%) in drinking water	EGCG reduced incidence of HG-PIN 100% to 17% at 12 weeks*	2007
			EGCG decreased epithelial cell proliferation by 54% in VP* EGCG increased the apoptotic index in the VP (394%) but not DLP* EGCG decreased AR in VP (51%) but not in the DLP at 12wks* Testosterone, DHT, and estradiol did not change at 12 or 28 weeks* EGCG decreased IGF-1 in the VP (30%) and DLP (31%)* and IGF-1R in the VP (42%) but not the DLP* EGCG decreased p-ERKS 1 and 2 by 45% and 57%* EGCG decreased COX-2 and iNOS by 24% and 77% in the VP*	
(Scaltriti et al., 2006)				
C57BL	EGC (5.5%)	GTC[b] (0.3%) in drinking water	An 8-gene signature analyzed by qPCR gene profiling discriminated between GTC responsive and GTC resistant TRAMP mice (8 gene signature tag included CLU, ODC, OAZ, AdoMetDC, SSAT, H3, Gas-1, and GAPDH)**	2006
	EC (12.2%) EGCG (51.9%)			
(Adhami et al., 2004)				
C57BL/TGN	Epigallocatechin-3-gallate (62%)	GTP[c] (0.1%) in drinking water	GTP decreased IGF-1 to IGFBP-3 ratios by 70 to 83% in DLP**	2004
	Epicatechin-3-gallate (24%)		GTP decreased VEGF expression in DLP by 34% (16 wks)*, 42% (24 weeks)** and 74% (32 weeks)***	
	Epigallocatechin (5%) Epicatechin (6%)		GTP decreased MMP-2 expression in DLP by 68% (24 wks)***, and 53% (32 wks)** GTP decreased PI3K by 67–79%**, p-Akt (Thr308) by 65%** and p-ERK1/2 by 50–62%**	
(Caporali et al., 2004)				
C57BL/6xFVB	EGC (5.5%), EC (12.2%)	GTC [b] (0.3%) in drinking water	GTC decreased palpable tumors from 20/20 to 0/20 at 24 weeks	2004
	EGCG (51.9%), ECG (6.1%) Caffeine (<1%)		GTC decreased clusterin expression during PCa onset and progression	
(Gupta et al., 2001)				
C57BL/6	Epigallocatechin-3-gallate (62%)	GTP[c] (0.1%) in drinking water	GTP reduced prostate growth by 44% (20 wks) and 42% (30 wks) as determined by MRI	2001
	Epicatechin-3-gallate (24%) Epigallocatechin (5%) Epicatechin (6%) Caffeine (~1%)		GTP group had a 5% decrease in body weight compared to non-transgenic controls†	
			GTP increased the tumor free survival of TRAMP mice by as much as 50% remain tumor free up to week 40.*** GTP increased median survival to 68 weeks compared to 42 weeks***	

[a] Roche,

[b] Isolated by investigators,

[c] Natural Resources & Products;

[†] authors suggest this “may be due to the result of more tumor growth and hyper proliferation of the accessory sex organs in the abdominal region that occurs in TRAMP mice.”

* $p < 0.05$,

** $p < 0.01$,

*** $p < 0.001$;

Abbreviations: AR = androgen receptor, VP = ventral prostates, DLP = dorsolateral prostate, DHT = dihydrotestosterone Clu = clusterin, ODC = ornithine decarboxylase, OAZ = ornithine decarboxylase antizyme, AdoMetDC = adenosylmethionine decarboxylase, SSAT = spermidine/spermine N1-actetyl-transferase, H3 = histone H3, Gas1 = growth arrest specific gene 1, GAPDH = glyceraldehydes 3-phosphate dehydrogenase, CLU = clusterin.