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## Chemopreventive Effects of Tea in Prostate Cancer: Green Tea vs. Black Tea

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### Abstract

The polyphenol compositions of green tea (GT) and black tea (BT) are very different due to post-harvest processing. GT contains higher concentrations of monomeric polyphenols, which affect numerous intracellular signaling pathways involved in prostate cancer (CaP) development. BT polymers, on the other hand, are poorly absorbed and are converted to phenolic acids by the colonic microflora. Therefore, after consumption of GT higher concentrations of polyphenols are found in the circulation while after BT consumption the phenolic acid levels in the circulation are higher. The majority of in vitro cell culture, in vivo animal, and clinical intervention studies examine the effects of extracts of GT or purified (-)-epigallocatechin-3-gallate (EGCG) on prostate carcinogenesis. These studies provide strong evidence supporting a chemopreventive effect of GT, but results from epidemiological studies of GT consumption are mixed. While the evidence for a chemopreventive effect of BT is much weaker than the body of evidence with regard to GT, there are several animal BT intervention studies demonstrating inhibition of CaP growth. This article will review in detail the available epidemiological and human clinical studies, as well as animal and basic mechanistic studies on GT and BT supporting a chemopreventive role in CaP.

### 1 Introduction

The evidence for chemoprevention by any bioactive substance is drawn from a combination of epidemiological, animal and basic mechanistic studies as well as limited amounts of evidence from human intervention studies. This is particularly true for tea which is the second most commonly consumed beverage in the world after water. The vast majority of the tea consumed in the world is black tea (BT), comprising approximately eighty percent of all tea consumed [1]. Nonetheless, the scientific evidence for the chemopreventive activities of green tea (GT) is far more extensive than that available for BT. The key chemical differences between BT and GT result from post-harvest processing. During GT tea production the endogenous oxidase enzymes in tea leaves are inactivated by heating so that the green tea polyphenols (GTPs), including epigallocatechin gallate (EGCG), are preserved. In BT, natural oxidation after harvesting results in polymerization and formation of theaflavins and thearubigins with small amounts of EGCG remaining in BT [1]. After ingestion, both BT and GT undergo fermentation by normal colonic flora also known as the microbiome. This metabolism results in the formation of phenolic acids, which may be active in chemoprevention. Therefore, the key differences between GT and BT are that

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GTPs are found in higher concentration in the circulation after consumption of GT compared to BT. On the other hand, the phenolic acid levels in the circulation are higher after consumption of BT by comparison to GT. This article will review in detail the available epidemiological and human clinical studies, as well as animal and basic mechanistic studies on GT and BT supporting a chemopreventive role in prostate cancer (CaP). This review will also highlight the importance of investigating the bioavailability and metabolism of polyphenols in CaP chemoprevention.

## 2 Prostate cancer

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death among men worldwide, with 914,000 new cases and 258,000 deaths in 2008 [2]. More than half of these cases and deaths are expected to occur in more developed countries [2]. The highest country-specific age-standardized incidence rate (per 100,000 population) in 2002 was 124.8 in the USA, and the lowest in Bangladesh (0.3), in China (1.6) and in India (4.4) [3]. Much of the observed geographic variation in CaP incidence may be due to differences in prostate-specific antigen (PSA) testing, and the ability to detect latent CaP [2]. However, differences in the use of PSA testing cannot explain all of the international variation, since there was already more than a 50-fold difference in international CaP incidence rates across countries in 1980 before the PSA test was introduced [3]. This indicates that environmental factors have a substantial role in determining cancer risk. In support of an environmental influence it was observed that men born in Japan and immigrating to Hawaii assimilated the host country's cancer rate both in their lifetime and in succeeding generations [4]. Diet is probably one of the most important environmental risk factors for CaP. The CaP incidence is low in Asian countries, and one possible explanation is the high intake of soy, tea, fish, fruits and vegetables and the reduced intake of red meat and fatty foods by comparison to the Western Diet [5]. However, the incidence of CaP is increasing rapidly in Asian countries due to the rapid introduction of a Western lifestyle, especially in urban centers [5]. CaP is typically diagnosed in men over 50 years of age and the rate of growth and progression is typically slow, which makes CaP an ideal disease in which to study the utility of preventive strategies, including those resulting from changes in nutrition and lifestyle [6]. Due to the fact that most CaP treatments carry the risk of side effects, there is an increasing trend for men diagnosed with less advanced CaP to choose expectant management, also called active surveillance, which provides additional opportunities to study non-toxic chemopreventive strategies such as GT.

## 3 Green and black tea

Tea is the most commonly consumed beverage second only to water in the world. All different varieties of tea including white, green, oolong, black and pu-erh teas are manufactured from the leaves of *Camellia sinensis*. For the production of GT the leaves are heat-treated to retain the typical polyphenols, also known as flavan-3-ols, including (-)-epigallocatechin (EGC), (-)-epigallocatechin-3-gallate (EGCG), (-)-epicatechin (EC), and (-)-epicatechin-3-gallate (ECG) [1]. For the production of BT the leaves undergo fermentation in moist and warm conditions [1]. Endogenous enzymes enhance the formation of polymers such as theaflavin and thearubigen. Therefore, BT contains a relatively small amount of monomeric polyphenols (Table 1). Other differences are the higher content of theanine and lower content of caffeine in GT [7]. Worldwide, 78 percent of tea produced is BT. By contrast GT comprises 20% of tea production and is the preferred form in China and Japan, as well as a few countries in North Africa and the Middle East. On the other hand, BT is consumed in European countries, the US, India, and many Arabic countries. The main tea producing countries are China, India, Kenya, Sri Lanka, Turkey, Indonesia, and Japan (Food and Agriculture Organization of the United Nations—Production [FAOSTAT](#)).

GT has been studied extensively for its chemopreventive activities with regard to CaP [8-10]. After evaluating all the evidence it becomes clear that there is a strong role for GT in chemoprevention of CaP, but much more research is needed on the chemopreventive potential of BT. More clinical research is needed for both GT and BT.

#### 4 Animal studies

Convincing evidence exists showing that GT extracts (GTE) decrease tumor growth in a variety of animal models. However, there are very few animal studies using brewed GT, and BT has not been studied as often as GT. However, several investigations using BT extracts demonstrated an inhibition of CaP growth in mouse xenograft and a rat models [1;11;12]. The majority of mouse studies are summarized in the review by Johnson et al [8]. Mouse xenograft models used both androgen-dependent (LNCaP and CWR22Rv1) and androgen-independent (PC-3, LNCaP-R104, CWR22R) cell lines. Both demonstrated a decrease in tumor growth with administration of EGCG or GTPs (Table 2). We will highlight a few important studies. Two studies investigated whether inhibition of tumor growth by GT intervention depends on the stage of CaP development [13;14]. In the study by Harper et al. 0.06% EGCG in drinking water decreased tumor growth at 12 weeks but not at 28 weeks of age in transgenic adenocarcinoma of the mouse prostate (TRAMP) model by inhibiting proliferation, inducing apoptosis, decreasing androgen receptor, insulin-like growth factor-1 (IGF-1), IGF-1 receptor, phosphor-extracellular signal-regulated kinases (ERK) 1 and 2, cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) [14]. The study by Adhami et al. demonstrated that treatment of TRAMP mice with 0.1% of GTE extended tumor-free survival significantly when the intervention was initiated prior to week 28. In addition, a decrease in IGF-1, IGF-1 receptor, phosphatidylinositol 3-kinase (PI3K)/AKT/ERK was only observed when treatment was started prior to week 28 [13]. Another important mouse study explored the question of the GTE concentration necessary for chemoprevention in an androgen dependent xenograft model tumor model in nude mice [11]. The investigators determined that the administration of 0.05% of GTE in drinking water was associated with a significant extension in days to reach 1200 mm tumor volume but not at 0.01%. This was associated with a decrease in PSA, an increase in apoptosis (PARP, caspase, Bax, Bcl2) and a decrease in vascular endothelial growth factor (VEGF) [11]. However in a few mouse studies GT administration was not effective [15;16]. For example in the study by Zhou et al. an intraprostatic inoculation of male severe combined immune deficient (SCID) mice with the androgen-sensitive human LNCaP CaP cell line was used. Oral administration of brewed BT but not GT in drinking water demonstrated a significant decrease in tumor weight associated with decreased serum PSA [15]. China green and black leaf tea imported from Shanghai Tea Import was used at a concentration of 15 g of tea leaves per liter of water [15]. On a weight basis this is a much higher intake of BT than typical for humans. Another interesting xenograft mouse model included the subcutaneous injection of TRAMP-C1 cells with or without lipopolysaccharide (LPS) in C57/Bl mice [16]. 0.6% GTE (59% EGCG) was administered in drinking water starting three days prior to tumor injection. GTPs did not inhibit tumor growth. However, LPS-induced recruitment of inflammatory polymorphonuclear phagocytes (PMNs) significantly decreased tumor growth, which was inhibited by GTP administration [16].

Most mouse studies investigating the chemopreventive and therapeutic effects of GT were performed using the TRAMP model and using the chemical EGCG or GTEs. TRAMP mice express the rat probasin (PB)-SV40 early gene (T/t antigen) construct under prostate specific control of the minimal rat probasin promoter and display mild to severe hyperplasia of the prostate epithelium, resembling prostatic intraepithelial neoplasia (PIN) by 6-12 weeks of age. Between 10 to 16 weeks well-differentiated neoplasia is generally observed, between 18-24 weeks of age all of the mice will display primary tumors, and by week 30 will display

metastases to distant sites [17]. Table 2 gives an overview of the TRAMP tea intervention studies. Most of the studies used GTE enriched in EGCG. The lowest effective concentration was 0.1% GTE in drinking water. In most studies GTPs were administered starting at 4 to 8 weeks of age. When GT was started at later points in time, the effect on tumor progression was decreased [13;18]. This could indicate that GT has more of a preventive effect earlier in transgenic tumor progression and less of a therapeutic effect once tumors are established. Moreover, not all investigations using TRAMP mice demonstrated protection. A study by Teichert et al. used 0.05% GTPs with unknown EGCG content and did not show a decrease in tumor weight [19]. Another study by Morey Kinney et al. administered orally 0.1% GTPs with 35% of EGCG and did not show a decrease in tumor progression [20]. In the same study no effect on DNA methylation in the prostate of TRAMP mice was found after administration of 0.1-0.6% GTPs in drinking water.

Few rat studies have been performed to investigate the chemopreventive effect of GT. One study by O'Sullivan et al. showed a decrease in tumor progression of 50% compared to water control but no decrease in tissue oxidative DNA damage marker, 8-hydroxydeoxyguanosine (8-OHdG). However manganese superoxide dismutase (MnSOD) protein expression was increased by the tea treatment [21].

Animal models clearly provide rapid answers by comparison to clinical studies, and serve a useful purpose in highlighting potential actions and interactions of candidate chemopreventive substances such as tea. However, there is some question as to how these studies relate to human benefit. Many of the studies are done with subcutaneous injection of tumor cells into an immune-impaired host and do not replicate the complex microenvironment of the human prostate gland. Nonetheless, the xenograft tumors are invaded by host immune and stromal cells and demonstrate tumor angiogenesis and elements of metastasis in appropriate model systems. Therefore, they do recapitulate elements of human CaP. Ultimately human intervention studies provide the best quality of evidence for the chemopreventive potential of tea.

## 5 Human epidemiological studies

As summarized in Table 3, twelve population studies, including five case-control and seven cohort studies, have been published evaluating the association of tea consumption with CaP. Among these population studies four evaluated the use of GT alone, two evaluated GT and BT, one evaluated only BT and five did not define the type of tea. The studies analyzing “tea” from Western countries presumably examine BT since this is the most common tea consumed in Western countries. Among the cohort studies, one GT study showed a protective effect in advanced CaP [22] and one BT study showed a protective effect in localized CaP associated with “tea” consumption [23]. Two GT cohort studies in Japan showed no association, one GT and BT cohort study from Hawaii in men with Japanese ancestry showed no effect and two cohort studies not defining the type of tea (Canada, USA) showed no effect (Table 3).

Among the case control studies one GT study from China showed a protective effect [24]. One tea study from Canada, most likely investigating BT, showed a protective effect and another study from Japan investigating GT and BT showed a trend to protective effect [25]. However there were two case control studies from Italy and Canada with “tea” not showing an association [26;27].

**The following cohort studies provide evidence for a positive association with the intake of GT and a reduced incidence of CaP**

The cohort study by Kurahashi et al. used the Japan Public Health Center-based cohort with 49,920 men aged 40-69 years assessed GT consumption habit at baseline and followed participants for 11 years [22]. GT was not significantly associated with localized CaP, but demonstrated a protective effect for advanced CaP [odds ratio (OR)=0.52,  $p_{\text{trend}}=0.01$ ] in comparing men drinking 5 or more cups/day compared with those who consumed less than 1 cup per day. [22]. An earlier cohort study by Heilbrun et al. involving 7833 men of Japanese ancestry living in Hawaii observed a weak but significant negative association of BT consumption and CaP incidence, with relative risk (RR) being 0.6 for those consuming more than one cup of BT daily versus almost never [23].

**The following cohort studies fail to show any association of GT intake and prostate cancer incidence**

The study by Kikuchi et al. using the Ohsaki cohort with 19 561 men aged 40-79 followed a Japanese population for 7 years and found 110 incident cases of CaP. There was no protective effect of GT (OR=0.85,  $p_{\text{trend}}=0.81$ ) [28].

Another cohort of 7999 men of Japanese ancestry living in Hawaii showed a borderline significant increase in risk for GT consumption, OR = 1.47 (95% CI: 0.99–2.19), but no association for BT [29]. Another cohort study by Allen et al. of 18 115 men including 196 cases of CaP demonstrated that men who drank 5 or more cups of GT had a 29% non-significant increase in CaP risk compared to those who drank tea less than once per day, (OR=1.29,  $p_{\text{trend}}=0.16$ ) [30].

**The following case control studies provide evidence for a positive association with the intake of GT and a reduced incidence of CaP**

The case control study from Southern China included 130 cases and 274 controls and provided information on duration, quantity and frequency of usual tea consumption [24]. Among the cases 55.4% were tea consumers compared to 79.9% of the controls. The CaP risk declined with increasing frequency, duration and quantity of GT consumption. The adjusted OR was 0.28 for tea drinking vs. non-tea drinking [24]. A slight reduction in CaP risk was also reported by a larger Canadian case-control study involving 617 cases and 637 population controls [31]. An OR of 0.70 (95% CI: 0.50–0.99) was reported with consumption of more than 500 g (approximately two cups) of tea per day [31].

**Other case control studies fail to show any association of GT intake and prostate cancer incidence**

The Japanese case control study by Sonoda et al. included 140 cases and controls and evaluated dietary habits based on a semi-quantitative food frequency questionnaire [25]. A modest non-significant reduction in risk (OR=0.67,  $p=0.3$ ) of the fourth vs. first quartile >10 cups vs. <1 cup of GT was found. However in this study only the intake of fish and natto were associated with a significant decrease in risk of CaP while the effect for tofu and all soy products were not significant [25]. Two more case control studies from Canada and Italy with 107 cases and 1623 cases, respectively, showed no association between tea consumption and CaP [26;27]. In summary evidence from population studies of the protective effect of tea and CaP is not conclusive. The variability between population studies is most likely based on the fact that the majority of publications seeking an association between tea consumption and the risk of CaP did not consider the type of tea consumed, the method of tea preparation and the tea polyphenol content, which is dependent on the method of preparation. Our own study of commercially available green teas in the United States

showed a large variation in GTP content [32]. Most of the studies showing a decrease in CaP risk were performed in Asian countries (Japan and China) or in Hawaii with men of Japanese descent. It should be noted that the failure to demonstrate an association of CaP incidence with the intake of tea should not be taken as proof of a lack of any association. As already indicated, population studies depend on numerous lifestyle variables which often cannot be adequately accounted for in analysis and can lead to false associations or failure to demonstrate associations. Intervention studies in humans also have numerous limitations discussed below and may also not yield conclusive evidence.

## 6 Human intervention studies

Data from two intervention studies in patients with localized CaP and two in patients with hormone refractory CaP have been published [33-36]. The first intervention study of localized CaP, performed in Italy, showed that GTPs are effective in delaying progression of premalignant lesions to CaP [33]. 60 men with high-grade prostate intraepithelial neoplasia (HG-PIN) in the baseline biopsy were randomized to either 600 mg of a decaffeinated GTE containing 51.8% of EGCG or placebo daily. At the end of one year repeat biopsy samples were taken and men in the placebo group had a 30 percent incidence of CaP compared to only 3 percent in the group receiving the GTE [33]. Serum PSA showed a non-significant trend to decrease in GTE-treated men at 9 and 12 months. A significant improvement was observed for the international prostate symptoms score. GTE administration also reduced lower urinary tract symptoms, suggesting that GTPs might be helpful in treating benign prostate hyperplasia (BPH). A two year follow up assessment was published in 2008 in a letter to the editor of European Urology [37]. Only 9 participants from the placebo-arm and 13 from the GTE-arm underwent a third biopsy sample collection. Despite the high drop-out rate the two arms remained balanced and large enough for statistical analysis. Two further cancer diagnoses appeared in the placebo arm and one in the GTE-arm. This indicates that overall, even after suspension of the GTE treatment, the GT-arm experienced an almost 80% reduction in CaP diagnosis compared to the placebo group [37]. In the second smaller intervention trial with localized CaP 25 men diagnosed with stage I, II, or III CaP, who were scheduled for prostatectomy consumed 4 capsules of Polyphenon E daily containing a total daily dose of 800 mg of EGCG [34]. The average intervention time was 4-6 weeks. Only one patient reported mild nausea related to the Polyphenon E intake. No adverse effects on liver function were observed. A significant decrease in serum PSA, hepatic growth factor (HGF), vascular endothelial growth factor (VEGF), insulin growth factor 1 (IGF-1) and ratio of IGF-1 to insulin growth factor binding protein 3 (IGFBP-3) was found [34]. In addition two intervention studies from Canada and the US investigating hormone refractory CaP showed a very limited protective effect on CaP by consumption of GTE [35;36]. In one study 6g of a pulverized GT powder which contained sugar, citric acid and flavoring was administered [36]. However no information was provided about the GTP content of this GT product. Only one participant of 42 showed a decrease in PSA level. The second intervention study with hormone refractory CaP administered a dose of 250 mg of GTE containing 75% GTPs twice daily [35]. Nine patient of 15 consuming the GTE for more than 2 months had progressive disease and six showed an apparent slowing of disease progression with a slow rise in PSA serum level. However, there were no “responders” as per the traditional definition of a PSA drop of greater than 50%. There were no control groups in either of the two studies. Unfortunately no clear conclusion can be drawn from the studies of hormone refractory disease due to lack of information on the GTP content in the first study [36] and the use of a relatively low dose in the second study [35]. The results of the intervention studies support the findings from animal studies that GT is more effective in prevention and early stages of CaP and less effective in hormone refractory disease.

## 7 Bioavailability and metabolism of tea polyphenols

The limited bioavailability and extensive metabolism of tea polyphenols after absorption provides a challenge to their utilization for chemoprevention [38]. Tea polyphenols are mainly absorbed from the small intestine. The absorption is regulated by multidrug resistance-associated protein transporter (MRP) and monocarboxylate transporter (MCT) [38]. MRP1 is located at the basal membrane and MRP2 at the apical membrane. GTPs are taken up into the epithelial cells and metabolized to glucuronides, sulfates and methyl metabolites [39]. Both GTPs and metabolites can be transported to the intestinal lumen or into the vascular system [38]. In humans and mice the rate of conjugation depends on the chemical structure of the GTPs. Gallated polyphenols such as EGCG and ECG are found in the circulation in the free form whereas nongallated polyphenols circulate mostly in conjugated form [40]. In addition all GTPs undergo methylation catalyzed by catechol-*O*-methyltransferase (COMT) [41]. Non-gallated polyphenols are excreted through the kidney into the urine, whereas gallated polyphenols are not found in the urine and have been demonstrated to be excreted through the enterohepatic circulation [40].

Human prostate tissue concentrations have been determined by our laboratory in men who participated in a phase II tea intervention study at the University of California Los Angeles. Men consumed 6 cups of GT or BT 3-8 weeks prior to prostatectomy. The 6 cups of GT provided 571 mg of EGCG, 291 mg of EGC, 75 mg of EC and 89 mg of ECG daily. Tissue aliquots collected after prostatectomy from men consuming GT contained EGCG, 4''-*O*-MeEGCG and ECG (Table 5) [42]. No GTPs were found in tissue from men in the BT or control groups. Participants collected urine samples during the intervention. Urine samples from men consuming GT contained EGC, 4'-*O*-MeEGC and EC (Table 6). Urine samples from men consuming BT contained 100 fold lower amounts of the same GTPs. No GTPs were found in the control group consuming only water [42]. In a prior pilot study, also designed as a preprostatectomy trial, a Darjeeling BT was used, which contained higher amounts of GTPs [43]. In this human study no theaflavins were found in the human prostate after BT consumption. However, when administering a very high concentration of decaf. BT extract (5%) mixed into the diet to C57BL/6 mice we demonstrated that theaflavins can be absorbed into liver, prostate, small intestine and colon [43].

Due to the high rate of EGCG-methylation in human prostate tissue, we investigated the bioactivity of the methyl metabolite of EGCG. We demonstrated that methylation of EGCG decreased its pro-apoptotic and nuclear factor kappa B (NFκB) inhibitory activities [42]. Similar observations were made by other investigators, who found that methylation of EGCG and ECG decreased their proteasome-inhibitory activity [44]. As shown in Table 5 and 6 about 50% or more of EGCG and EGC found in human prostate and urine are in the methylated and less active form. Similar methylation rates were found in tissues of mice drinking brewed GT as drinking water (Figure 2) (unpublished data). GTP concentrations were similar in mouse and human tissues. However in human tissue only EGCG, 4''-MeEGCG and ECG were found, whereas the mouse tissue contained EC, EGC, 4'-MeEGC, EGCG and 4''-MeEGCG. After the intragastric administration of 164 μmol/kg (equivalent to about 2.2 mg per 30 g mouse) EGCG to mice similar EGCG tissue concentration were found with ( $C_{max}$ ) for EGCG (nmol/g) 0.09-0.2 in prostate, 0.03-0.1 in liver, 0.002-0.01 in lung, 45±14 in small intestine and 7.9±2.4 in colon [45]. A study by Meng et al. found EGCG and 4'4''-DiMeEGCG in liver, kidney and small intestine, plasma, urine and feces [46]. As substrates of methyltransferases, GTPs are able to inactivate methylating enzymes such as COMT and DNA methyltransferase (DNMT1). There is the potential that GT may inhibit carcinogenesis by limiting methylation of DNA and affecting the expression of proteins that stimulate proliferation [47;48]. The inhibition of DNMT1 activity by GTPs in cell culture has been demonstrated to lead to demethylation of the CpG islands in the promoter regions

and the reactivation of methylation-silenced genes such as p16INK4a, retinoic acid receptor beta, O6-methylguanine methyltransferase, human mutL homolog 1, and glutathione S-transferase-pi (GSTp1) [48]. Since CaP is commonly associated with hypermethylation and silencing of GSTp1 it could be possible that GT intervention may assist in reactivation of GSTp1 [49;50] thus increasing its antioxidant activity and inhibiting tumor growth.

Due to the limited absorption of GTPs and BT theaflavins, the GTPs remaining in the small intestine are transformed in the colon by the microflora to phenolic acids. In a study designed to examine the effects of GT and BT digestion products, an artificial colon containing human colonic microflora (TNO, Holland) was incubated with GT and BT concentrates [51]. The major phenolic acids found in the artificial colon content after GT and BT digestion were 3-methoxy-4-hydroxyphenylacetic acid, 4-hydroxyphenyl acetic acid, 3,4- dihydroxyphenylacetic acid, 3,3-hydroxyphenylpropionic acid, 2,4,6-trihydroxybenzoic acid [51].

The composition of BT varies strongly depending on the growing region and manufacturing conditions [32]. For example, Darjeeling tea contains higher amounts of EGCG compared to regular BTs [32]. Most in vivo BT intervention studies have analyzed plasma GTP concentrations. A study by Mulder et al. demonstrated that theaflavins are only minimally bioavailable [52]. 800 mg of theaflavin, equivalent to 30 cups of BT, was administered to two volunteers leading to a plasma concentration of 1 µg/L at 2 hours [52]. It is unlikely that theaflavin and thearubigins directly contribute to the chemopreventive effects of BT. Biological effects of BT consumption most likely are due to the GTPs and phenolic acids resulting from colonic metabolism. Therefore, in vitro evidence of potential molecular targets of BT theaflavins will not be discussed as this research is unlikely to be relevant to CaP chemoprevention. However, the bioactivity of the microflora products may be more relevant to the chemopreventive effects of BT. Further research is needed to determine whether the tissue concentrations of phenolic acids are sufficient to exhibit a chemopreventive effect. Preliminary research indicated that the IC<sub>50</sub> concentration to inhibit cell proliferation in HCT116 colon cancer cells at 75 µmol/L is much higher than the achievable tissue concentrations [51].

BT frequently is consumed in combination with a small amount of milk. The majority of investigations demonstrated that the addition of milk did not decrease the bioavailability of GTPs from BT [53;54]. However, one study by Reddy et al demonstrated a decrease of plasma GTPs when BT was consumed with milk [55]. The same study also demonstrated that the plasma antioxidant activity was not affected by milk [55]. Other studies showed mixed results on the effect of BT and milk combination on the antioxidant activity. The study by Kyle et al. 2007 demonstrated no decrease of the plasma antioxidant activity but the study by Ryan et al. demonstrated a decrease in the in vitro antioxidant of BT when combined with milk [54;56].

## 8 Molecular targets of GTPs in prostate cancer

Polyphenolic botanical extracts such as GTPs exert their effects on tumor growth through multiple mechanisms reviewed below.

### 8.1 Antioxidant/prooxidant activity

Most molecular targets have been investigated in mechanistic studies conducted in cell culture. The stability of tea polyphenols decreases with increasing pH above pH 7. Extensive studies by Neilson et al. demonstrated that in alkaline conditions EGCG undergoes dimerization and autoxidation involving the B-ring to form homodimers or heterodimers with other tea polyphenols such as EGC, forming theasinensins [57]. This process leads to



the concurrent formation of hydrogen peroxide [58] and results in prooxidant actions of EGCG in cell culture [59]. Hydrogen peroxide in cell culture exhibits many activities similar to EGCG which makes the interpretation of results from studies of EGCG complex. Therefore many results from cell culture experiments will need to be confirmed in animal studies. The antioxidant activity of tea polyphenols has been summarized in a review by Lambert and Elias (2010) [60] and is also described in a chapter by Lambert et al. in this special edition.

To date, no human studies have been published demonstrating antioxidant activity of GTPs in CaP. Unpublished data from our laboratory demonstrated a decrease in oxidative DNA damage (ratio of 8-OHdG/guanosine) and oxidative protein damage (carbonyl protein) in LAPC4 prostate xenograft tumors in SCID mice consuming brewed GT in place of drinking water (manuscript in preparation). The GT contained 700 mg/L (0.07%) of total GTPs including 634 mg (0.063%) of EGCG.

Since tissue concentrations of GTPs are very low, a direct chemical antioxidant effect is unlikely. However, EGCG may act indirectly through stimulating the transcription factor, erythroid 2p45 (NF-E2)-related factor 2 (Nrf2) [61]. Nrf2 mediates the expression of key antioxidant enzymes through the antioxidant-response element (ARE) [62]. These antioxidant enzymes include glutathione reductase (GSR), glutathione peroxidase (GPX), glutathione-S-transferase (GST), glutamate-cysteine ligase (GCL), manganese superoxide dismutase (MnSOD), NAD(P)H:quinone oxidoreductase (NQO1), heme oxygenase-1 (HO-1), thioredoxin reductase1 (TRX1) and peroxiredoxin (PRX1) [63]. It has been demonstrated that Nrf2 and members of the glutathione-S-transferase (GST) mu family are extensively suppressed by gene methylation in human CaP [64;65]. Using the TRAMP transgene and Nrf2 knockout murine models it was demonstrated that the loss of Nrf2 initiates a detrimental cascade of reduced GST expression, elevated ROS levels and ultimately DNA damage associated with tumorigenesis [65;66]. It has been demonstrated that treatment with EGCG was able to stimulate nuclear accumulation, ARE binding and transcriptional activity of Nrf2 in MCF10A breast cancer and Caco-2 colon cancer cells [61;67].

## 8.2 Apoptosis and cell cycle arrest

GTPs have been demonstrated to induce cell cycle arrest at G1 phase and induce apoptosis in androgen dependent LNCaP and androgen-independent PC-3 and DU145 cells [68-70]. However different mechanisms have been held responsible. For example EGCG-induced apoptosis in human prostate carcinoma LNCaP cells (p53 wildtype) was mediated via modulation of two related pathways: (a) stabilization of p53 by phosphorylation on critical serine residues and p14ARF-mediated downregulation of murine double minute 2(MDM2) protein, and (b) negative regulation of NFκB activity, thereby decreasing the expression of the proapoptotic protein Bcl-2 [68]. The altered expression of Bcl-2 family members triggered the activation of initiator caspases 9 and 8 followed by activation of effector caspase 3 followed by poly (ADP-ribose) polymerase cleavage and induction of apoptosis [68]. In DU145 (p53 mutant) and PC-3 (p53 null), apoptosis was induced through different mechanisms such as through an increase in reactive oxygen species (ROS) formation and mitochondrial depolarization [69]. These observations were further supported by the fact that the rank order of the effects of different GTPs in growth suppression, apoptosis induction, ROS formation and mitochondrial depolarization were similar (i.e. ECG > EGCG > EGC > EC) [69]. In another study EGCG treatment of LNCaP and DU145 cells resulted in significant dose- and time-dependent (i) upregulation of the protein expression of WAF1/p21, KIP1/p27, INK4a/p16, and INK4c/p18, (ii) down-modulation of the protein expression of cyclin D1, cyclin E, cdk2, cdk4, and cdk6, but not of cyclin D2, (iii) increase in the

binding of cyclin D1 toward WAF1/p21 and KIP1/p27, and (iv) decrease in the binding of cyclin E toward cdk2 [70].

### 8.3 Insulin-like growth factors and binding proteins

The insulin-like growth factors (IGF-1 and IGF-2) and their binding proteins (IGFBP) play central roles in cell growth, differentiation, survival, transformation and metastasis. The biological effects of the IGFs are mediated by the IGF-1 receptor (IGF-1R), a receptor tyrosine kinase homologous to the insulin receptor (IR) [71]. IGF-1 interacts with IGF-1R to induce a series of ligand-mediated receptor activation and mitogenic responses, including PI3K/AKT and RAS/RAF/MAPK cascade, controlling cell survival and cell proliferation, respectively. Activated AKT also stimulates NF $\kappa$ B transcriptional activity and the mammalian target of rapamycin (mTOR) [72]. Epidemiological observations indicate that circulating IGF-1 levels are positively associated with increased risk of CaP [72]. A study by Li et al demonstrated that EGCG is a highly potent inhibitor ( $IC_{50}=14 \mu\text{mol/L}$ ) of IGF-1R tyrosine kinase activity and malignant cell growth [73]. Furthermore, it was found that IGF-1R autophosphorylation in the presence of increasing ATP concentrations was unaltered by EGCG treatment [73]. Mouse studies using the TRAMP model demonstrated the inhibition of IGF-1 signaling [14;74]. In addition, the above-mentioned human Polyphenon E intervention study by McLarty et al confirmed a decrease in IGF-1 and the ratio of IGF-1 to IGFBP-3 [34].

### 8.4 Inflammation

Inflammation is implicated as a major risk factor of CaP. Population studies have found an increased relative risk of CaP in men with prior histories of prostatitis [75]. Benign prostatic hyperplasia (BPH), a condition which often precedes and coexists with CaP, demonstrates signs of inflammatory response. Specifically, almost all human BPH specimens showed inflammatory infiltration and high expression of pro-inflammatory cytokines, including interleukin-17 (IL-17) that promotes stromal growth and chronic inflammation [76]. Interestingly, inflammatory pathways, including the cyclooxygenase-2 (COX-2) and NF $\kappa$ B, are over-expressed in human prostate adenocarcinomas compared with normal prostate tissues and targeting these inflammatory pathways have shown promise as an intervention strategy for CaP [75;77]. In vitro EGCG treatment of LNCaP cells with 20-80  $\mu\text{mol/L}$  was associated with a decrease in DNA binding activity of NF $\kappa$ B. Furthermore, EGCG decreased TNF $\alpha$  (a known inducer of NF $\kappa$ B)-induced NF $\kappa$ B activity. In addition, a decrease in the protein levels of the p65 subunit of NF $\kappa$ B in nuclear lysates of LNCaP cells treated with EGCG was observed. This observation indicated that reduced availability of NF $\kappa$ B subunits in the nucleus may be responsible for the decreased transcriptional activity [68]. NF $\kappa$ B can modulate the transcriptional activation of genes associated with cell proliferation, angiogenesis, metastasis, tumor promotion, inflammation and suppression of apoptosis via the regulation of gene expression of genes such as bcl-2, bcl-x1, cIAP, survivin, TRAF, COX-2, MMP-9, iNOS and cell cycle-regulatory components. [78]. NF $\kappa$ B also amplifies inflammatory signals, including COX-2 and pro-inflammatory cytokines, such as IL-6, by acting as a transcriptional activator [77]. Cyclooxygenase is an enzyme involved in the synthesis of prostaglandins from arachidonic acid. Overexpression of COX-2 has been implicated in many pathologic conditions, including cancer. It has been demonstrated that EGCG inhibits COX-2 without affecting COX-1 expression at both the mRNA and protein levels, in androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells [79].

### 8.5 Angiogenesis

Solid tumors cannot grow beyond 2-3 mm in diameter before the diffusion limit of oxygen (100-200  $\mu\text{m}$ ) is reached and hypoxia develops. Therefore both the growth and metastasis of

tumors are dependent on the formation of new blood vessels (angiogenesis) [80]. A switch to the angiogenic phenotype requires a local change in balance between proangiogenic factors and angiogenic inhibitors [81]. Proangiogenic factors such as VEGF can be stimulated by hypoxia via the hypoxia-responsive transcription factor HIF-1 $\alpha$  [82]. Immunohistochemical studies have confirmed the upregulation of HIF-1 $\alpha$  and VEGF in areas of human CaP compared with normal prostate and benign prostatic hyperplasia (BPH) [83]. The expression and activation of HIF-1 $\alpha$  is tightly regulated by cellular oxygen concentration. Administration of GTPs and EGCG in drinking water to TRAMP mice was associated with tumor inhibition, decreased VEGF and angiogenesis [74]. In cell culture experiments the situation is more complicated. For example Thomas et al. demonstrated that 20-40  $\mu$ mol of EGCG inhibited prolyl hydroxylation of HIF-1 $\alpha$ , thus preventing HIF-1 $\alpha$  and pVHL interaction in PC-3 cells. However they also demonstrated a stimulation of Hif-1 $\alpha$  protein levels at normoxic condition [84]. This most likely is related to the proteasome inhibitor activity of EGCG. The effect of EGCG on VEGF secretion has been demonstrated in multiple cancer models [85;86]. In stromal fibroblasts derived from primary prostate cancers treatment with 10  $\mu$ mol/L of EGCG decreased VEGF secretion into the medium [34]. In TRAMP mice consuming 0.1% GTE in drinking water, serum VEGF was decreased significantly at 24 weeks [74]. An effect on serum VEGF was also observed in the human Polyphenon E intervention study of McLarty et al. [34].

### 8.6 Cancer metastasis

Multiple cellular signaling pathways have been involved in the processes of cancer cell invasion and metastasis. Matrix metalloproteinases (MMP) play a crucial role in the development and metastatic spread of cancer. One of the earliest events in the metastatic spread of cancer is the invasion through the basement membrane and proteolytic degradation of the extracellular matrix proteins, such as collagens, laminin, elastin and fibronectin etc, and non-matrix proteins. MMPs are the important regulators of tumor growth, both at the primary site and in distant metastases [87]. Treatment of DU145 cells with 5-40  $\mu$ g/L of EGCG resulted in dose-dependent inhibition of induced pro-MMP-2 and pro and active forms of MMP-9 concomitant with marked inhibition of phosphorylation of ERK1/2 and p38 [87]. The HGF/c-Met pathway is another important regulator of signaling pathways implicated in the processes of invasion and metastasis of most human cancers, including CaP. Exposure of DU145 prostate tumor cells to hepatic growth factor (HGF) stimulates the activation of c-Met and downstream PI3-kinase and MAPK pathways, leading to increased scattering, motility, and invasion, which was prevented by the addition of 5  $\mu$ mol/L of EGCG [88]. The polyphenol epigallocatechin-3-gallate also affects lipid rafts in the cell membrane to block activation of the c-Met receptor in CaP cells. The c-Met inhibitory activity of EGCG may be facilitated through altering lipid raft structures [88].

### 8.7 Cancer stem cells

Epithelial-mesenchymal transition (EMT) induction in cancer cells results in the acquisition of invasive and metastatic properties [89]. Recent reports indicate that the emergence of cancer stem cells (CSCs) occurs in part as a result of EMT through cues from tumor stromal components [90;91]. Cancer stem cells undergoing metastasis usually express EMT markers (vimentin, slug, snail and  $\beta$ -catenin). A study by Tang et al. in 2010 indicated that human CaP cell lines contain a small population of CD44+CD133+ cancer stem cells and their self-renewal capacity was inhibited by EGCG [92]. Furthermore, EGCG inhibited the self-renewal capacity of CD44+a2b1+CD133+ CSCs isolated from human primary prostate tumors, as measured by spheroid formation in suspension. EGCG induced apoptosis by activating caspase-3/7 and inhibiting the expression of Bcl-2, survivin and XIAP in CSCs. Furthermore, EGCG inhibited EMT by inhibiting the expression of vimentin, slug, snail and nuclear  $\beta$ -catenin, and the activity of the LEF-1/TCF responsive reporter, and also retarded

CSC's migration and invasion, suggesting the blockade of signaling involved in early metastasis.

### 8.8 Androgen receptor

Androgens not only play an important role in the development and function of the prostate but they are also intimately involved in the development and progression of CaP. Within the prostate, testosterone is converted to the more potent androgen dihydrotestosterone (DHT) via the action of the 5 $\alpha$ -reductase enzyme. DHT is the primary prostatic androgen and promotes the growth and survival of normal, hyperplastic and malignant prostate tissues. Throughout the different stages of CaP (PIN, localised, recurrent, and metastatic) there is an increase in expression of 5 $\alpha$ -reductase particularly in localised high-grade carcinoma [93]. In *in vitro* experiments it has been demonstrated that EGCG inhibited 5 $\alpha$ -reductase with an IC<sub>50</sub> of 15  $\mu$ mol/L [94]. Prostate tumor growth is primarily regulated by androgen binding and transcription signals of the androgen receptor (AR). Androgen-deprivation therapy (ADT), which suppresses the binding of androgens to the androgen receptor (AR), has been the mainstay of treatment for recurrent CaP after primary treatment. Despite suppression of prostate tumor growth, ADT eventually fails, leading to hormone-refractory tumor growth, even though functional AR is often present and even overexpressed in hormone-refractory CaP cells [95]. EGCG suppresses cell proliferation, PSA expression, and AR mRNA and transcriptional activity of AR in androgen dependent and independent LNCaP sublines [96-98]. In addition, in cell culture studies it has been demonstrated that GTE and EGCG, but not EC, inhibited both basal and kinase-stimulated testosterone production in rat Leydig cells [99]. Further *in vivo* experiments with oral supplementation with GT are needed to confirm the effects of EGCG on hormone production.

## 9. Conclusion

Strong evidence from *in vitro* and *in vivo* animal studies supports the role of GT in CaP prevention. However, prior to assuming that these benefits translate to humans, several points need to be considered. First, as pointed out in this review, most of the *in vitro* studies do not take the pro-oxidant activity of EGCG at alkaline pH into consideration. With the elimination of the "hydrogen peroxide" effect, much higher concentrations of GTPs would be necessary to induce the same effects. Second, it appears that mouse tissue bioavailability of GTPs is considerably different from human tissue. Therefore the bioavailability in human tissue may be more limited and the potential of GTPs more limited.

Nonetheless, human population studies provide some supportive evidence for a decrease in risk of CaP associated with increased consumption of tea. Evidence is stronger for GT compared to BT. However, for the evidence to be convincing, population studies showing a beneficial effect of tea need to be replicated. The evidence from human clinical trials demonstrating a decrease in the rate of tumor progression from PIN to adenocarcinoma together with evidence of a decrease in serum markers of tumor progression provide strong support for the preventive actions of GT in localized CaP [33;34]. Further intervention studies are needed to demonstrate the effect of brewed tea, which is consumed in amounts relevant to the demonstrated intakes in epidemiological studies. Currently our group is conducting a phase II clinical trial investigating the effects of the consumption of 6 cups of GT or BT prior to prostatectomy on biomarkers of CaP. This trial will be completed in 2011 (Clinical Trial ID: NCI-2010-00973).

Overall, epidemiological and human clinical studies, as well as animal and basic mechanistic studies on GT and BT support a chemopreventive role in CaP with an emphasis on GT, but more research efforts at many levels is needed.

## 9 References

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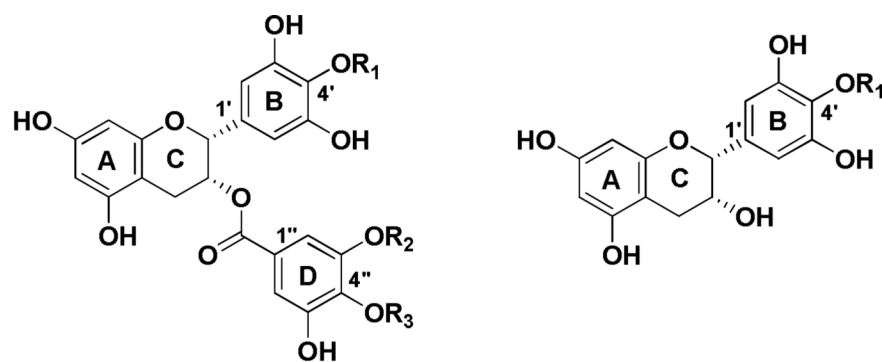
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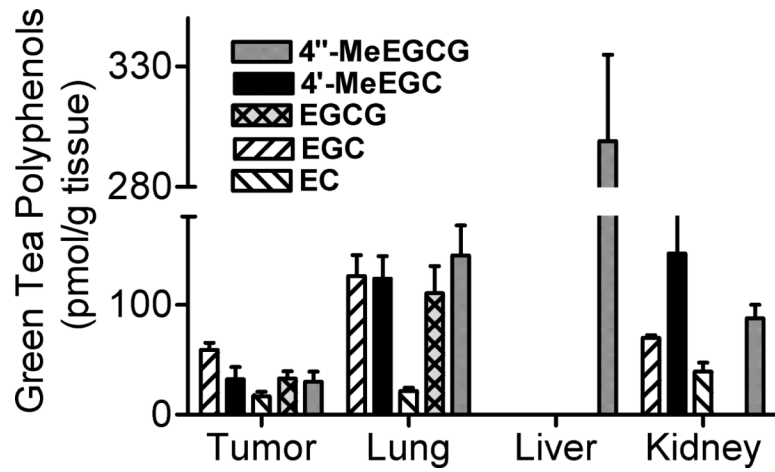
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	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>		R <sub>1</sub>
EGCG	H	H	H	EGC	H
4''-MeEGCG	H	H	CH <sub>3</sub>	4'-MeEGC	CH <sub>3</sub>

**Figure 1.**  
Chemical structure of methylated and non-methylated EGCG and EGC.



**Figure 2.**

Tissue concentrations of GTPs were determined in SCID mice inoculated s.c. with LAPC4 androgen-dependent prostate cancer cells. Drinking water was replaced with brewed green tea containing 0.07% GTPs freshly prepared every 2 days. 10 weeks after tumor cell inoculation mice were sacrificed and tumor, lung, liver and kidney tissue was collected and analyzed by high performance liquid chromatography with Coularray electrochemical detection (mean±std; n=5)[107].

**Table 1**

Composition of green and black tea solids (percent) [1].

Constituents	Green Tea (%)	Black Tea (%)
Flavan-3-ols	30-42	3-10
Flavonols	5-10	6-8
Other Flavonoids	2-4	--
Theogallin	2-3	--
Gallic acid	0.5	--
Quinic acid	2.0	--
Theanine	4-6	0-2
Methylxanthines	7-9	8-11
Theaflavin	--	3-6
Thearubigin	--	12-18

Table 2

Studies of prostate cancer prevention and treatment in animal models.

Animal Model	Chemopreventive Agent	Outcome	Reference
Androgen-sensitive LNCaP intraprostatic in SCID mice	Oral brewed GT and BT: 15g leaves/L of water	↓tumor growth, ↓DHT with GT and BT, ↓PSA with BT not GT	Zhou JR et al. 2003 [15]
Androgen-sensitive CWR22Rv1 in nude mice	Oral 0.05 and 0.01% of GTE (62% EGCG) when tumor was 400mm <sup>3</sup>	↓tumor growth, ↑apoptosis, ↓VEGF, ↓PSA	Sidiqui IA et al. 2006 [11]
Androgen-sensitive CWR22Rv1 in nude mice	Oral 1.25% BT extract	↓tumor growth, ↑apoptosis, ↓VEGF, ↓PSA	Sidiqui IA et al. 2006 [11]
CWR22R androgen-independent in nude mice	EGCG and EGCG-P	↓tumor growth, ↑apoptosis, ↓angiogenesis ↓PSA	Lee SC et al. 2008 [100]
s.c.TRAMP-C1 cells into C57/Bl male mice	Oral 3d prior to tumor 0.6% of GTE (59% EGCG)	No effect on tumor growth	Sartor L et al. 2004 [16]
TRAMP C57BL/6 mice	Oral 0.1% GT extract (62% EGCG) starting at 8 wks of age	At 20 wks 44% inhibition of tumor growth, 30 wks 42%, ↓serum IGF-1, ↑IGFBP-3, ↑apoptosis	Gupta S et al. 2001 [101]
TRAMP C57BL/6 mice	Oral 0.1% GTE (62% EGCG) starting at 8 wks of age	↓tumor growth, ↓serum IGF-1, ↑IGF BP-3, ↓PI3K, ↓Akt, ↓ERK1/2, ↓VEGF, ↓urokinase plasminogen activator, ↓matrix metalloproteinases	Adhami VM et al. 2004 [74]
TRAMP C57BL/6 mice	Oral 0.3% GTE (51.9% EGCG)	8-genes differentiated between prostate of wt from transgenic mice and TRAMP+GTP responsive from non-responsive mice	Scaltriti M et al. 2006 [102]
TRAMP C57BL/6 mice	Oral 0.3% GTE (51.9% EGCG)	At 24 wks only 20% developed tumors in GT group, ↓MCM7	McCarthy S et al. 2007 [103]
TRAMP C57BL/6 mice	Oral 0.06% EGCG starting at 5 weeks	At 12 weeks ↓tumor growth, but not at 28 wks. ↑apoptosis, ↓AR, ↓serum IGF-1, ↓ERK1/2, ↓COX-2, ↓iNOS	Harper CE et al. 2007 [14]
TRAMP C57BL/6 mice	Oral 0.1% GTE (62% EGCG) starting at 4 wks of age	↓NFκB, IKKa, IKKb, RANK, NIK, STAT-3 with a trend to decrease over time (8-32 wks)	Siddiqui IA 2008 [18]
TRAMP C57BL/6 mice	Oral 0.1% GTE (62% EGCG) starting at 6, 12, and 18 wks of age	Tumor-free survival of 38 wks (GTP at 8 wks), 31 wks (GTP at 12 wks) and 24 wks (GTP at 18 wks) vs 19wks in control	Adhami VM 2009 [13]
TRAMP C57BL/6 mice	Oral 0.05% GTE at 4 wks of age	No effect on tumor weight and urine 8-OHdG	Teichert F 2008 [19]
TRAMP C57Bl/6:FVB 50:50	Oral 0.1% of GTE (35% EGCG) at 4 or 6 wks of age and oral 0.1-0.6% GTPs	No effect on tumor progression. At 12 weeks of 0.1-0.6% GTPs no effect on DNA methylation status	Morey Kinney SR et al. 2009 [20]
Lobund Wistar rats	Oral 0.2% of GT (freeze dried – 10% EGCG)	50% less tumors compared to water cntr, no effect on 8-OHdG in prostate, ↑MnSOD	O'Sullivan J et al. 2008 [21]
Nobel rats CaP induced with testosterone	Oral 2% GT and 200 g soy protein/kg diet	Only GT+soy ↓prostate hyperplasia, ↓NFκB p50 binding activity, ↓TNF-a, ↓IL-6, ↑apoptosis	Hsu A et al. 2010 [104]
Wistar rats s.c. injection of testosterone (5mg/kg bwt)	Oral 0.5, 1, 1.5% (w/v) BT extract	↓oxidative stress induced by testosterone, ↓SOD, ↓GST, ↓GR, ↓Cat, ↓lipid peroxidation	Siddiqui IA et al. 2005 [12]

**Table 3**

Population studies investigating the prevention and treatment of prostate cancer using green and black tea.

Location	Type of Study	Daily Dose	Odds Ratio	Reference
Green tea, Japan	Cohort Study, advanced CaP N=49,920, cases=404	≥ 5 cups, protective	0.6 (p=0.01)	Kurahashi N et al. 2008 [22]
Black tea, Hawaii	Cohort of men of Japanese decent n=7833, cases=149 >58 yrs	Once per day, > 10 years, protective	0.6 (p=0.04)	Heilbrun LK et al. 1986 [23]
Green tea, Japan	Cohort Study, n=19561, cases=110	≥5 cups, no association	0.85 (P=0.81)	Kikuchi N et al. 2006 [28]
Green tea, Japan	Cohort Study N=18115, cases=196	No association	P=0.16	Allen NE et al. 2004 [30]
Green tea and black tea, USA (Hawaii)	Cohort Study n=7999, cases=174 Japanese ancestry	No association	GT ever vs never 1.47 BT ever vs never 0.83	Severson et al. 1989 [29]
Tea, Canada	Cohort Study, n=3400, cases=145	>500 mL, No association	1.02	Ellison et al. 2000 [105]
Tea, UK (London)	Prospective Cohort n=14085, cases=185	>10 compared to <4, no association	0.8 (p=0.3)	Kinlen LJ et al. 1988 [106]
Green tea, China	Case control cases=130, controls=274	Protective effect	0.28	Jian L et al. 2004 [24]
Green and black tea, Japan	Case control cases=140, controls=140	≥10 cups protective trend, not significant	GT 0.67 (p=0.3) BT 1.5	Sonoda T et al. 2004 [25]
Tea, Canada	Case control cases=617, controls=637	>500 ml, protective	0.7 (p=0.05)	Jain MG et al. 1998 [31]
Tea, Italy	Case control cases=107, Controls=6147	>1 cup no association	0.9	LaVecchia C et al. 1992 [26]
Tea, Canada	Case Control Study (cases=1623, controls=1623)	> 4 cups/day, No association		Villeneuve et al. 1999 [27]

**Table 4**

Human intervention studies using green tea extracts in localized and advanced prostate cancer.

Location	Type of Study	Effect	Daily Dose	Reference
Green tea extract, Italy	Intervention Study (n=60) 1 year	Decreased progression from PIN to CaP	600 mg GTE (310.8 mg EGCG)	Bettuzzi S et al. 2006 [33]
Green tea extract, Italy	1 year follow up	Significantly lower rate of CaP	No intervention	Brausi M et al. 2008 [37]
Polyphenon E, US	Intervention Study (n=25)	Decreased serum PSA, HGF, VEGF	1300 mg Polyphenon E (800 mg EGCG)	McLarty J et al. 2009 [34]
Green tea extract, Canada	Intervention study (n=19) in hormone refractory CaP	No effect	500 mg GTE (112.5 mg EGCG)	Choan E et al. 2005 [35]
Green tea powder, USA	Intervention study (n=42) in hormone refractory CaP	PSA decreased by 50% in one out of 42 subjects, no effect. Grade 1 and 2 toxicity in 69% and no side effects in 31% of participants	6 g instant green tea powder in 6x 1g doses in hot water	Jatoi A et al. 2003 [36]



**Table 5**

Concentration of GTPs in human prostate tissue and the percent occurring in free, glucuronidated or sulfated form from men consuming 6 cups of GT daily for 3-6 weeks (mean±std; n=8) [42].

GTP	Total (pmol/g prostate)	Glucuronide (%)	Sulfate (%)	Free form (%)
EGCG	42.1±32.4	23.2	10.6	66.2
4"-O-methyl EGCG	38.9±19.5	13.3	10.1	76.6
ECG	17.8±10.1	11.3	9.8	78.9

**Table 6**

Concentration of GTPs in human urine from men consuming either 6 cups of GT or BT for 3-6 weeks ( $\mu\text{mol/g}$  creatinine; mean $\pm$ std, n=8) [42].

	EGC	EC	4'-MeEGC
Baseline	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Week 3 GT intervention	7.8 $\pm$ 3.9	6.9 $\pm$ 3.4	12.4 $\pm$ 5.9
Week 3 BT intervention	0.016 $\pm$ 0.02	0.011 $\pm$ 0.01	0.023 $\pm$ 0.03