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Chapter 13

Green Tea Catechins for Prostate Cancer Chemoprevention

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Additional information is available at the end of the chapter

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1. Introduction

1.1. Prostate cancer: Opportunity for prevention

Prostate cancer (PCa) is the most commonly diagnosed cancer and second most common cause of cancer deaths in American men. The American Cancer Society estimates that there will be 233,000 new cases of prostate cancer in the United States (US) in 2014, and 29,480 men will die from this disease. [1] The initiation and progression of PCa involves a complex series of events. During progression, genetic changes and loss of cellular control are observed as cell phenotypes change from normal to dysplasia (prostatic intraepithelial neoplasia or PIN), severe dysplasia (high-grade PIN or HGPIN), atypical small acinar proliferation (ASAP) or focal glandular prostatic atypia (FGA), [2, 3] clinically localized and finally to metastatic disease. [2, 4 - 7] The frequency of HGPIN as well as latent PCa is evenly distributed, suggesting that external factors such as diet, physical activity, and other lifestyle factors are important in the transformation from these early stages into more aggressive, clinical cancer. [2, 4 - 9] Although early screening and detection has been used historically as strategies for PCa prevention, these recommendations have been a subject of much debate in recent years. Although screening using serum prostate-specific antigen (PSA) has not been shown to significantly reduce either PCa-specific or overall mortality, it has been linked to the substantial overtreatment of clinically insignificant, potentially indolent tumors. [10 - 12] With questions about value of prostate-specific antigen (PSA)-based screening, [10 - 12] few prevention options are available for asymptomatic men who are at high risk for PCa. To address the urgent need for alternative preventive strategies, hormonal agents including the 5-alpha-reductase inhibitors finasteride and dutasteride, which block the conversion of testosterone to dihydrotestosterone, have been evaluated for PCA chemoprevention. [13 - 15] Although a reduction in PCa incidence of 23%–

25% was observed with these agents, [13, 15] concerns about higher incidence of aggressive cancers and toxicities have limited their clinical adoption, establishing the need to identify alternative chemoprevention agents [14] with a more favorable safety profile. These features of prostate cancer, namely, high prevalence, long latency, significant mortality and morbidity, availability of HGPIN and ASAP as intermediate predictive stages of progression, and urgent need for alternative strategies for prevention other than screening, provide the most promise and best opportunity for evaluating agents for chemoprevention.

2. Cancer chemoprevention

Chemoprevention refers to the inhibition of preinvasive and invasive cancer and its progression or treatments of identifiable precancers. [16, 17] Successful chemopreventive interventions require a thorough evidence-based understanding of the mechanism and hallmarks of carcinogenesis. Novel technologies, methods, and approaches in genomics, metabolomics, and proteomics have enabled this field of research. In order for chemopreventive efforts to be successful, it is imperative to employ these innovative methods and approaches to develop pharmacologic agents (including botanicals/biologicals) to reverse or halt the process of carcinogenesis. Chemopreventive agents include antipromotion and antiprogression compounds that could prevent or stop the survival, growth, and dissemination/metastasis of cells that are already committed to become malignant. [16, 17]

3. Botanicals as agents for cancer chemoprevention

Although several targeted "smart" drugs have emerged over the past decade, it is clear that diseases like cancer have an etiology based on perturbations of multiple signaling pathways. Thus, targeting multiple pathways may represent a more effective approach to cancer control. [18 - 20] In addition, the monotargeted "smart" drugs are associated with high cost and produce numerous side effects. These drawbacks of monotargeted drugs underscore the importance for the development of multitargeted, innocuous, inexpensive, and readily available botanicals for the prevention of cancer. [20] Botanicals have been shown to influence multiple biochemical and molecular cascades that inhibit mutagenesis and proliferation, induce apoptosis, and suppress the formation and growth of human cancers, modulating several hallmarks of carcinogenesis, with a significantly superior safety profile than most agents evaluated to date. Multiple botanicals have been identified and appear promising for PCa chemoprevention. [31]

The objective of this chapter is to review and summarize the most current literature focusing on GTC for prostate cancer chemoprevention based on evidence from laboratory, *in vitro*, and *in vivo* studies and clinical chemoprevention trials.

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4. Green tea catechins and prostate cancer chemoprevention

4.1. Epidemiological evidence of the role of GTC and prostate cancer prevention

Several reviews summarizing epidemiological evidence have suggested a protective effect of tea consumption against human cancers of the breast, cervix, colon and rectum, gallbladder, liver, lung, nasopharynx, pancreas, prostate, stomach, ovary, and uterus. [32 - 35] Twenty percent of green tea is consumed in Asian countries such as China, Japan, and Korea, where populations drinking green tea consistently demonstrate lower PCa risks. Epidemiological studies, however, have been mixed, potentially due to confounding factors such as variations in tea consumption(salted, hot), dietary, tobacco and alcohol use, genetic differences, and recall bias. [36, 50] The risk for PCa increases in Asians who migrate to the US if original dietary habits are abandoned. There is epidemiological evidence that Asian men consuming green tea have lower PCa risk, potentially due to exposure over their lifetime that prevents transformation or progression to later stages of prostate carcinogenesis. The conflicting epidemiological results have been attributed to confounding factors that include consumption of salted or very hot tea, geographical location, use of tobacco and alcohol, other dietary differences, and lack of standardization of quantities and compositions of the tea products consumed. In a case–control study conducted in China during 2001–2002, prostate cancer risk declined with increasing frequency, duration, and quantity of green tea consumption [OR = 0.28 (95% CI = 0.17–0.47)], showing a dose–response relationship. [39] Four to five times more men die of CaP in the US than that in Japan. [36] It also appears that the onset of CaP occurs later in life and/or CaPs grow more slowly in Japanese populations compared to Western populations, which may be attributed to the consumption of GTC and soy products. Thus, the potential preventive properties of GTP in prostate cancer, as demonstrated by evidence from epidemiological studies although limited, appear promising.

4.2. Preclinical evidence of the role of GTC and prostate cancer prevention

Several published preclinical studies using green tea, green tea leaves, green tea extracts, GTP mixtures, green tea catechin (GTC) mixtures, and the individual catechins have demonstrated chemopreventive efficacy in several cancers. [51 - 57] Using the TRAMP mice model, Gupta et al. [51] were able to demonstrate that oral infusion of GTP extract at a human achievable dose (equivalent to six cups of green tea per day) significantly inhibits CaP development and increases survival in these mice. When 0.1% GTP (weight/volume) was provided as the sole source of drinking water to transgenic adenocarcinoma mouse prostate (TRAMP) mice 8–32 weeks of age, the result was (i) substantial reduction in the tumor incidence, tumor burden, and delay in metastasis as assessed by magnetic resonance imaging (MRI); (ii) substantial reduction in prostate (by 64%) and genitourinary (GU) (by 72%) weight; (iii) substantially decreased serum insulin-like growth factor-I (IGF-I) and restored to normal insulin-like growth factor binding protein-3 levels (IGFBP-3); and (iv) marked decrease in the expression of proliferating cell nuclear antigen (PCNA) in the prostate compared with control (water-fed) TRAMP mice. Furthermore, GTP consumption caused significant apoptosis of CaP cells, which possibly resulted in reduced dissemination of cancer cells, thereby causing the inhibition of

CaP development, progression, and metastasis of CaP to distant organ sites. However, in another similar animal model, epigallocatechin gallate (EGCG) only slightly reduced these levels. [52] These observations may be attributed to the pharmacokinetic properties of EGCG, which has relatively low oral bioavailability. [52] These inconsistencies could also be explained by differential doses, different methods of infusion, duration of intervention, and inadequate timing of castration necessary to observe changes in markers of progression and the antioxidant property of EGCG. Oral administration of GTPs (*vs.* pure EGCG) at 500 mg/kg/day in drinking water to TRAMP mice is expected to cause a higher systemic exposure compared to gavage and may explain the protective effects observed by Gupta et al. [51] compared with Suttie et al. [52] Earlier preclinical trials [54, 57, 107] have observed decreasing effectiveness of GTC with advancing stage of PCa using a TRAMP mouse model. We investigated the safety and efficacy of PolyE administered with the goal to reduce the progression of CaP in TRAMP mice which is an established model of CaP. [56] In this study, 119 TRAMP and 119 C57BL/6J mice were treated orally with one of three doses of PolyE (200, 500, and 1000 mg/kg/day) in drinking water ad libitum, replicating human achievable doses. Safety and efficacy assessments in our study were performed when mice were 12, 22, and 32 weeks old. The number and the size of tumors in the PolyE group were significantly decreased compared with the control group (water-fed). In water-fed 32-week-old control TRAMP mice, prostate carcinoma metastasis to distant sites was observed in 100% of mice (8/8), compared with 13% of mice (2/16) treated with high-dose PolyE during the same period. Furthermore, PolyE treatment significantly inhibited metastasis in TRAMP mice in a dose-dependent manner ($P = 0.0003$). Long-term (32 weeks) treatment with PolyE was safe and well tolerated with no evidence of toxicity in C57BL/6J mice. PolyE similar to other GTC formulations has been observed to be effective chemopreventive agents in preventing the progression of prostate cancer in TRAMP mice with no toxicity in these mouse models. Our findings provide additional preclinical evidence for the safety and chemopreventive effect of PolyE in preventing metastatic progression of prostate cancer. [56] Preclinical studies, including our recent work with PolyE, have consistently demonstrated chemopreventive efficacy in PCa, significantly delaying primary tumor incidence and tumor burden, with reduction in markers of proliferation and potent and selective *in vitro* and *in vivo* proapoptotic activity on PCa cells.

4.3. Potential mechanism by which GTC modulates prostate carcinogenesis:

A body of research evidence indicates that tea and tea compounds reduce the growth of several human cancer cell lines *in vitro*, including stomach, lung, prostate, colon, leukemia, oral tumor, liver, breast, and cervix, as well as HPV-immortalized cervical epithelial cells. Among the constituents of GTCs, laboratory studies have identified EGCG as the most potent chemopreventive agent that affects a number of molecular processes including induction of apoptosis and inhibition of tumor growth and angiogenesis with no significant effect on benign controls. [58 - 62] EGCG has been reported to affect several cancer-related proteins, including p27, Bcl-2 or Bcr-Abl oncoproteins, Bax, matrix metalloproteinases (MMP-2 and MMP-9), [63] androgen receptor, EGF receptor, activator protein 1 (AP1), and some cell cycle regulators. [64 - 66]

In their recent review of signaling pathways that are affected by green tea polyphenols, Khan et al. [67] reported that various pathways mediated via mitogen-activated protein kinases (MAPK) signaling were affected, including extracellular-signal-related kinases (ERK1/2), c-Jun N-terminal kinases/stress-activated protein kinases (JNK1/2/3 or SAPKs), p38 MAPK, ERK3/4, ERK5, and ERK7/8. Ultimately, MMP-2 and MMP-9 expressions were affected by EGCG via inhibition of phosphorylation of ERK1/2 and p38 pathways. Since MMP-9 and MMP-2 are known biomarkers of invasion and metastasis, the inhibition of their expression leads to inhibition of prostate cancer spread. Insulin-like growth factors (IGF) exert multiple effects on glucose, fat, and protein metabolism and play important roles in regulating cell proliferation, differentiation, apoptosis, and transformation. PI3K/Akt and Ras/MAPK pathways can be activated via IGF-signaling, supporting cell proliferation. GTCs are known to suppress cellular signaling via the IGF-axis, thus affecting cell proliferation. Cyclooxygenase (COX) is a rate-limiting enzyme in the prostaglandin biosynthesis. COX-2 can be activated via NF-κB signaling pathway, leading to inflammation and cell proliferation. EGCG was shown to inhibit COX-2 expression at both the mRNA and the protein levels in the prostate, thus slowing down the cancer growth. Finally, EGCG have a notable effect on cell cycle arrest. Gupta et al. [68] have earlier reported that treatment of CaP cell lines LNCaP and DU145 with EGCG caused cell cycle disruptions and reduced proliferation of cells due to down-regulation of various cyclins as well as altered binding to CDKs. Treatment of human CaP cell lines LNCaP and PC-3 with GTP caused the inhibition of class I HDAC activity, leading to cell cycle arrest and induction of apoptosis.

Yang et al. [69] have recently reported that phenolic groups of EGCG can directly bind to multiple molecules due to their hydrogen bonds. The molecules of interest include B-cell CLL/lymphoma 2 protein (BCL2), which has antiapoptotic properties, leading to induction of apoptosis. Some other EGCG binding targets include glucose-regulated protein 78 kDa, vimentin, IGF-1R, and peptidylcis/trans isomerase. Via this mechanism, EGCG can modulate the formation of reactive oxygen species (ROS) as well as affect other molecular pathways described above.

Rizzi et al. [70] reported that Poly E induced cell cycle arrest at the G_0/G_1 checkpoint for PNT1a prostate cell lines (modeling early stage disease) and G_2/M for PC3 cells (modeling late stage disease). The authors showed that in the model of an early stage disease, autophagy was the first mechanism to activate in response to endoplasmic reticulum stress (ERS). After that stage, which lasted approximately 12 h, activation of caspases occurred, indicating anoikis cell death. In the model of an aggressive CaP, Poly E induced severe ERS which eventually led to GADD153/CHOP activated Puma, a BH3-only protein, committing cells to necroptosis, a programmed caspase-independent mechanism of cell death. These results may aid in the identification of novel targets and strategies aimed at sensitizing apoptosis-resistant cells to alternative death pathways.

Hagen et al. [71] reported that EGCG induced apoptosis in PC3 cells, via the caspase 9-dependent mechanism. Furthermore, EGCG, both alone and in combination with cisplatin, promoted the expression of the proapoptotic splice isoform of caspase 9, and it modifies the

alternative splicing of caspase 9, favoring the proapoptotic isoform. The latter finding suggests that EGCG may affect the alternative splicing of cancer-associated genes *in vivo*.

Connors et al. [72] have previously proposed a mechanistic model according to which GTCs antitumor action in prostate cancer acts through proteasome. GTC-induced inhibition of chymotrypsin-like activity of the proteasome results in the accumulation proteasome targets p21, p27, Bax, and IκBα. The accumulation of cell cycle regulators p21 and p27 result in G1 cell cycle arrest, whereas the accumulation of the proapoptotic protein, Bax, contributes to cell apoptosis. The oncogenic transcription factor, NFκB, is down-regulated, presumably by the elevation of IκBα, its intrinsic inhibitor. This results in the reduced expression of NFκB target genes, antiapoptotic, Bcl-xL and Bcl-2, cell cycle regulators, cyclin D and cyclin E, and metastasis-related genes, VEGF, angiopoietin 1/2, MMPs, and uPA. Reductions in cyclins D and E, Bcl-2, and Bcl-xL further drive the processes of cell cycle arrest, decreased cell proliferation, and apoptosis, respectively. Additionally, the reduction in metastasis-related genes inhibits tumor cell invasion and metastasis.

Based on their studies of GTP in cell culture systems, Adhami et al. [63] were able to demonstrate that EGCG in GTP induces apoptosis, cell growth inhibition, and cyclin kinase inhibitor WAF-1/p21-mediated cell cycle dysregulation.Using cDNA microarrays, they also observed that the EGCG treatment of LNCaP cells results in the induction of genes that functionally exhibit growth-inhibitory effects and repression of genes that belong to the G-protein signaling network. When oral feeding of GTP was the sole source of drinking fluid for TRAMP mice, a significant inhibition of VEGF, MMP-2, and MMP-9 was demonstrated, suggesting antimetastatic and antiangiogenic properties of GTP that may affect CaP progression. [63] Bettuzzi et al. have validated these findings, showing that oral administration of GTP to TRAMP mice reduced CaP onset from 100% to 20% [94] mediated by induction of clusterin (CLU) expression, which is potently up-regulated during prostate gland involution [95] but down-regulated in human CaP specimens [73, 74] and exerts antiproliferative [75] and proapoptotic activity [76 - 79] in PNT1a and PC-3 cells.

EGCG potently and selectively inhibits the proteasome activity in intact human CaP cells and consequently accumulates IkBα and p27 proteins, leading to growth arrest (Figure 1). [59 - 61] ECCG has been shown to decrease NF-κB DNA binding and abrogates NF-κB activation by DNA-damaging agents. Our group also reported that EGCG was able to inhibit NF-κB activation through stabilization of IκBα. [58 - 61] NF-κB is a eukaryotic transcription factor involved in the regulation of COX-2 and many other genes. [79] The constitutive activation of NF-κB has been reported in many tumors, [80, 81] associating it with progression of epithelial cells, including prostate, toward malignancy. This inhibition of proteasome activity by EGCG occurred at or near physiological concentrations *in vitro* (IC50 = 0.1−0.2 mM) and *in vivo* (1−10 mM) at the concentrations found in the serum of green tea drinkers. [59 - 61] The ubiquitin/proteasome system plays an important role in the degradation of cellular proteins. This proteolytic system includes two distinct steps: ubiquitination and degradation. [82, 83] The 26S proteasome is a high molecular weight (2.4MDa), ATP-dependent, multiprotease complex. [84 - 86] This complex, which exists in both the cytoplasm and nucleus, is composed of a catalytic subunit (20S) and regulatory subunits. [87] The 20S catalytic subunit contains at least

three enzymatic activities, chymotrypsin-like (prefers Tyr or Phe at the P1 site), trypsin-like (prefers Lys or Arg), and glutamyl peptidyl hydrolytic-like (prefers Asp or Glu). [88] The inhibition of only the chymotrypsin-like activity has been tightly associated with apoptosis induction. Most substrates that are degraded by the proteasome are first covalently modified with ubiquitin (a 76 amino acid polypeptide). [82] Many substrates of the proteasome are proteins that are involved in the regulation of cell cycle progression and apoptosis. [86] For example, the proteasome degrades regulators of cyclin-dependent kinases (CDK) such as cyclins and the CDK inhibitors p21waf and p27kip as well as the CDK phosphatases CDC25 A, B, and C. The proteasome also degrades IκBα, an important inhibitor of the tumor survival factor NF-κB. Many physical (i.e., radiation), chemical (cancer chemotherapeutic agents), viral, and biological (cytokines and growth factors) agents induce phosphorylation, ubiquitination, and subsequent degradation of IκBα by the proteasome, freeing up NF-κB to translocate to the nucleus and to modulate genes involved in proliferation, invasion, and tumor survival. [89, 90] For example, NF-κB up-regulates the antiapoptotic protein Bcl2 and down-regulates the proapoptotic protease caspase 8. Therefore, by inhibiting the proteasome, IκBα will accumulate, which will inhibit NF-κB from promoting tumor survival. The proteasome is also responsible for degrading the tumor suppressor p53. Many tumor cells inactivate p53 by overexpressing an E3 ligase called mdm2, which binds p53 and ubiquitinates it for degradation by the proteasome. [82, 83] In human tumors, which overexpress mdm2, the inhibition of the proteasome is predicted to induce tumor cell apoptosis by accumulating p53. CEP1612, a dipeptidyl proteasome inhibitor, was able to rapidly induce apoptosis in all the human cancer cell lines tested, including breast, prostate, leukemia, lung, bone, brain, and head and neck, but not in human normal fibroblasts and normal breast cells. [85, 91] They also reported that proteasome inhibition was sufficient to overcome apoptotic protection by Bcl-2 or Bcr-Abl oncoprotein. [91] Recently, it has been reported that proteasome inhibition accumulates Bax (but not Bcl-2) protein in mitochondria, resulting in increased ratio of Bax/Bcl-2, associated with cytochrome *c* release and apoptosis induction. [92] It has also been reported that during TNF-α-induced apoptosis, Bcl-2, but not Bax, protein is degraded through ubiquitin/proteasome-dependent pathway, [93] which also increased the Bax/Bcl-2 ratio. Therefore, selectively degrading one or more Bcl-2 family proteins by the proteasome should change the ratio of pro- to antiapoptotic proteins, which might contribute to the apoptotic commitment.

In summary, there is increasing experimental evidence that GTCs slow down prostate carcinogenesis via an umbrella of mechanisms and cellular pathways that work in concert to affect multiple hallmarks of cancer. The main pathways include proteasome inhibition, cell cycle arrest, inhibition of cell proliferation, induction of apoptosis, suppression of growth and invasion, and inhibition of metastasis. Further research should elucidate the exact sequence of cellular events induced by GTCs that lead to suppression of prostate malignancy.

4.4. Clinical experience: green tea polyphenols and prostate cancer

Several phase I studies, sponsored by the National Cancer Institute's Division of Cancer Prevention (NCI, DCP) and others, comparing the pharmacokinetics and safety of oral green tea, polyphenon E, and EGCG, have been completed and published. [96 - 99, 100] By conduct-

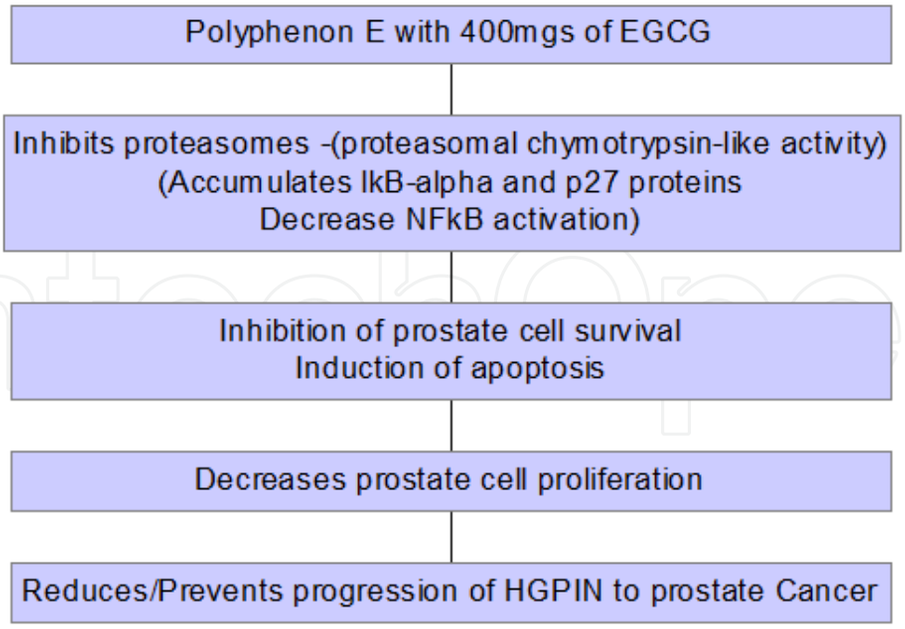

Figure 1. Modeling relative to the primary mechanism of Polyphenon E in Prostate Cancer

ing a phase I trial of oral green tea extract in adult patients with solid tumors, Pisters et al. [98] reported that a safe dose of green tea extract was equivalent to 7–8 Japanese cups (120 ml) of green tea three times daily for 6 months. They concluded that the side effects (neurological and gastrointestinal effects) of the green tea extract preparation were caffeine related, and not from EGCG. The average cup of green tea contains 10–50 mg of caffeine; therefore, overconsumption may have a stimulatory effect in some individuals. Thus, although green tea is practical, nontoxic, and has the potential to be developed for chemoprevention, one has to consume 8–10 cups to obtain these benefits and the side effects due to caffeine are a concern.

In a single-dose study sponsored by NCI, DCP, each subject received two single doses containing 200, 400, 600, or 800 mg EGCG provided by each of two different formulations (polyphenon E or a purified EGCG preparation) separated by a 2-week washout period. [96] Plasma EGCG levels increased with dose and formulation had no effect on EGCG pharmacokinetics. Although little EGCG circulated in conjugated form, EGC and EC were highly conjugated. In a completed multidose study, healthy subjects with sun-sensitive skin received 800 mg EGCG alone or as polyphenon E in one or divided daily doses for 4 weeks. [101] Adverse effects were predominantly mild gastrointestinal complaints. Plasma levels of EGCG were significantly higher in the 400 mg qd versus 400 mg bid dose group for both formulations. Plasma antioxidant levels and UV light-induced minimum erythema dose (MED) were unaffected by any treatment. In the third completed phase I study, the effect of fasting on pharmacokinetics was examined in healthy adults taking 400, 800, or 1200 mg EGCG as polyphenon E. Plasma levels of free EGCG were dramatically higher when taking polyphenon E in the fasting state compared to the fed state for all three dose levels; the average C_{max} increased more than 3.6-fold, and the average AUC increased more than 2.3-fold when taking polyphenon E on an empty stomach. In a study to test if the oral bioavailability of green tea

catechins can be enhanced when consumed in the absence of food, Chow et al. [97] observed that greater bioavailability of free catechins can be achieved by taking the polyphenon E capsules on an empty stomach after an overnight fast thus optimizing the biological effects of tea catechins. Recent studies including individual case reports have indicated several grade 1–2 AEs, including case studies of liver toxicities and rectal bleeding (personal communication from DCP), all of which indicate the need for continued monitoring of safety in well-designed clinical trials.

Bettuzzi et al. [102 - 103] completed a randomized clinical trial to assess safety and efficacy of GTCs for chemoprevention of CaP in men diagnosed with HGPIN. [73] Purity and content of GTCs preparations were assessed by HPLC (EGC 5.5%, EC 12.24%, EGCG 51.88%, ECG 6.12%, total GTCs 75.7%, caffeine <1%). After 1-year intervention with GTC tablets containing 600 mg EGCG/day, only one tumor was diagnosed among the 30 GTC-treated men (incidence: about 3%), while nine cancers were found among the 30 placebo-treated men (incidence: 30%). After 9 months of treatment, subjects taking GTC had a 17% decrease in total PSA values; otherwise, PSA values did not change significantly between the two arms of the study, probably because of high individual differences. No significant side effects were documented. As a secondary observation, they found that the administration of GTCs at this dose was also effective at reducing LUTS. However, other studies intervening in men with localized prostate cancer in the presurgical phase (from biopsy to prostatectomy) with GTC failed to observe chemopreventive benefit [104 - 106] observed in trials targeting earlier stages of prostate carcinogenesis (HGPIN). These early trials indicate that GTC may not exert a meaningful effect once diagnosed with prostate cancer and, consistent with earlier preclinical trials, [54, 104] have observed decreasing effectiveness of GTC with advancing stage of PCa using a TRAMP mouse model. In summary, evidence from phase I/II studies has demonstrated bioavailability and tolerance to GTC at doses ranging from 200 to 1200 mg per day and for a duration of 1 year with observation of chemoprevention effects in the early stages (HGPIN) of prostate carcinogenesis and not in the later stages. With few options available for the chemoprevention of early precursors of PCa, GTC shows promise to be further evaluated as chemoprevention agents targeting high-risk cohorts with HGPIN.

5. Conclusions and future directions

GTCs are promising agents for the chemoprevention of prostate cancer. Early observations indicate that GTCs at human achievable doses are most effective against early stage prostate carcinogenesis in preclinical and clinical trials and are attractive chemopreventive agents with a favorable safety profile. There is an urgent need to continue to identify chemopreventive agents to reduce the burden of cancer. However, it is just as critical to learn from the experience of past chemoprevention trials [108 - 115] that underscore the need for systematically characterizing these agents for cancer chemoprevention and defining their efficacy, safety, and mechanism of action using preclinical and early-phase work before undertaking phase III trials and ultimately translating the findings to clinical practice.

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