This article was downloaded by: *[University of Washington]*
On: *28 February 2010*
Access details: *Access Details: [subscription number 908957100]*
Publisher *Routledge*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK

Nutrition and Cancer
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t775653687

Review: Green Tea Polyphenols in Chemoprevention of Prostate Cancer: Preclinical and Clinical Studies

Naghma Khan [a]; Vaqar Mustafa Adhami [a]; Hasan Mukhtar [a]
[a] Department of Dermatology, University of Wisconsin, Madison, Wisconsin, USA

Online publication date: 10 November 2009

To cite this Article Khan, Naghma, Adhami, Vaqar Mustafa and Mukhtar, Hasan(2009) 'Review: Green Tea Polyphenols in Chemoprevention of Prostate Cancer: Preclinical and Clinical Studies', Nutrition and Cancer, 61: 6, 836 — 841
To link to this Article: DOI: 10.1080/01635580903285056
URL: http://dx.doi.org/10.1080/01635580903285056

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Nutrition and Cancer, 61(6), 836–841
Copyright © 2009, Taylor & Francis Group, LLC
ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635580903285056

Routledge
Taylor & Francis Group

Review: Green Tea Polyphenols in Chemoprevention of Prostate Cancer: Preclinical and Clinical Studies

Naghma Khan, Vaqar Mustafa Adhami, and Hasan Mukhtar
Department of Dermatology, University of Wisconsin, Madison, Wisconsin, USA

Downloaded By: [University of Washington] At: 21:03 28 February 2010

The prevention of prostate cancer (PCa) is a crucial medical challenge in developed countries. PCa remains surrounded by puzzles in spite of the considerable progress in research, diagnosis, and treatment. It is an ideal target for chemoprevention, as clinically significant PCa usually requires more than two decades for development. Green tea and its major constituent epigallocatechin gallate (EGCG) have been extensively studied as a potential treatment for a variety of diseases including cancer. In this review, we highlight the evidences of green tea polyphenols from preclinical and clinical studies in the chemoprevention/chemotherapy of PCa.

INTRODUCTION

Prostate cancer (PCa) is one of the most common cancers in men in the United States and is the second leading cause of male cancer death worldwide after lung cancer. The number of new PCa cases expected to be diagnosed in the United States alone in 2009 are 19,280, with an estimated 27,360 disease-related deaths (1). Therefore, it is essential to find strategies for the prevention of PCa. Death rates from PCa vary worldwide, with Westernized nations having the highest risk of incidence and death and Asian nations having the lowest. Many factors have been suggested to take part in the development of PCa, but the most consistent risk factors associated with an increased incidence rate of the disease are race, age, and family history of PCa (2,3). It is mostly unknown the extent to which the racial/ethnic differences affects variables in screening methods, environmental exposures, and/or hormonal and genetic factors. PCa results due to the accumulation of both genetic and epigenetic alterations that transform normal glandular epithelium to preneoplastic lesions and on to invasive carcinoma. Morphologically, PCa often reveals heterogeneity in histological grade within individual tumors and multifocal histogenesis within the prostate. In some cases, this heterogeneity may, in fact, be the result of multifocal tumorigenesis with multifocal tumors of varying grades growing closer together with the passage of time, finally culminating in the fusion of separate lesions (4). The identification of molecular markers specific to early and late events in PCa progression is critical for the development of improved detection and diagnostic strategies. PCa is an attractive and appropriate target for primary prevention because of its incidence, prevalence, and disease-related morbidity and mortality. PCa is an ideal candidate disease for chemopreventive intervention. First, it is a unique malignancy that generally grows very slowly, before symptoms arise and a diagnosis is finally established. Second, because of long latency period, it is typically diagnosed in men more than 50 yr of age.

Many dietary agents are being examined as potential PCa chemopreventive agents (5). The tea plant (*Camellia sinensis*) has been cultivated in Asia for thousands of years. Currently, more than two-thirds of the world population consumes this popular beverage. Green tea is manufactured by drying fresh tea leaves. It contains characteristic polyphenolic compounds, (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG) and (−)-epicatechin (EC) (6). Catechin, gallocatechin, epigallocatechin digallates, epicatechin digallate, 3-*O*-methyl EC and EGC, catechin gallate, and gallocatechin gallate are present in smaller quantities. EGCG appears to be the most powerful of all the catechins, with an antioxidant activity about 25–100 times more potent than that of vitamins C and E (7). Various in vitro and in vivo studies suggest that consumption of green tea polyphenols (GTP) is associated with decreased risk and/or slower progression of PCa (6,8). In this review, we discuss the studies of GTP in cell culture, animal models, and humans in the chemoprevention/chemotherapy of PCa.

CELL-CULTURE STUDIES

We have shown for the very first time that EGCG induced apoptosis and cell cycle arrest in many cancer cells without affecting normal cells (9), an observation that has been reproduced with similar effects in many cancer cells. We have recently shown that combination of EGCG and NS-398, a specific COX-2 inhibitor resulted in enhanced cell growth inhibition, apoptosis induction, expression of Bax, pro-caspase-6, and pro-caspase-9,

Submitted 1 May 2009; accepted in final form 24 August 2009.
Address correspondence to Hasan Mukhtar, Helfaer Professor of Cancer Research, Director and Vice Chair for Research, Department of Dermatology, University of Wisconsin–Madison, 4385 Medical Sciences Center, 1300 University Avenue, Madison, WI 53706. Phone: 608-263-3927. Fax: 608-263-5223. E-mail: hmukhtar@wisc.edu

Downloaded By: [University of Washington] At: 21:03 28 February 2010

and poly(ADP)ribose polymerase (PARP) cleavage, inhibition of peroxisome proliferator activated receptor (PPAR)-γ and inhibition of NF-κB compared with the additive effects of the two agents alone, suggesting a possible synergism (10). We have reported that EGCG sensitizes TRAIL-resistant LNCaP cells to TRAIL-mediated apoptosis through modulation of intrinsic and extrinsic apoptotic pathways. When combined with EGCG, Apo2L/TRAIL exhibited enhanced apoptotic activity in LNCaP cells accompanied by the upregulation of PARP cleavage and modulation of proapoptotic and antiapoptotic Bcl2 family of proteins. Pretreatment of cells with EGCG resulted in modulation of DR4/TRAIL R1, FADD, and c-FLIP. There was also a synergistic inhibition in the invasion and migration of LNCaP cells through inhibition in the protein expression of VEGF, uPA, and angiopoietin 1 and 2. The activity and protein expression of MMP-2, -3, and -9 and upregulation of TIMP1 in cells treated with a combination of EGCG and TRAIL was also observed (11). We have demonstrated using isogenic cell lines that EGCG activates growth arrest and apoptosis in prostate carcinoma cells primarily via p53-dependent pathway that involves the function of both p21 and Bax such that downregulation of either molecule confers a growth advantage to the cells (12). In androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells, EGCG inhibited COX-2 without affecting COX-1 expression at both the mRNA and protein levels (13). In a dose-dependent manner, EGCG was found to inhibit degradation of gelatin, degradation of type IV collagen in reconstituted basement membrane, and activation of MMP-2, but not pro-MMP-9, in a cell-free system (14). Both EGCG and theaflavins treatment was found to decrease the levels of PI3K and phospho-Akt and increase ERK1/2 in both DU145 and LNCaP cells (15). The high levels of fatty acid synthase activity in LNCaP cells was dose-dependently inhibited by EGCG, and this inhibition was paralleled by decreased endogenous lipid synthesis, inhibition of cell growth, and induction of apoptosis (16). We have earlier reported that EGCG-induced apoptosis in human prostate carcinoma LNCaP cells is mediated via modulation of stabilization of p53 by phosphorylation on critical serine residues and p14ARF-mediated downregulation of murine double minute 2(MDM2) protein, and negative regulation of NF-κB activity, thereby decreasing the expression of Bcl-2. EGCG-induced stabilization of p53 caused an upregulation in its transcriptional activity, thereby resulting in activation of WAF1/p21 and Bax. This altered expression of Bcl-2 family members triggered the activation of capsase-9 and 8 followed by activation of caspase-3 and cleavage of PARP (17). EGCG treatment of LNCaP and DU145 cells resulted in significant dose- and time-dependent upregulation of the protein expression of WAF1/p21, KIP1/p27, INK4a/p16, and INK4c/p18, downmodulation of the protein expression of cyclin D1, cyclin E, cdk2, cdk4, and cdk6, but not of cyclin D2, increase in the binding of cyclin D1 toward WAF1/p21 and KIP1/p27, and decrease in the binding of cyclin E toward cdk2 (18). It has been shown that ester bond-containing tea polyphenols, such as EGCG, potently and specifically inhibit the chymotrypsin-like activity of the proteasome in vitro and in vivo at the concentrations found in the serum of green tea drinkers. The inhibition of the proteasome by EGCG in several tumor and transformed cell lines resulted in the accumulation of two natural proteasome substrates, KIP1/p27 and IκBα followed by growth arrest in the G(1) phase of the cell cycle (19). Green tea catechins (GTC) and extract were found to suppress the growth and caused induction of apoptosis in human PCa DU145 cells through an increase in reactive oxygen species formation and mitochondrial depolarization (20). We have reported previously that EGCG negatively modulated PCa cell growth by affecting mitogenesis as well as inducing apoptosis, in a cell-type-specific manner, which may be mediated by WAF1/p21-caused G(0)/G(1)-phase cell-cycle arrest, irrespective of the androgen association or p53 status of the cells. EGCG treatment resulted in a dose-dependent increase of p53 in LNCaP cells carrying wild-type p53 but not in DU145 cells carrying mutant p53 (21). Pretreatment of the cells with GTP resulted in a significant inhibition of testosterone-caused induction of ornithine decarboxylase (ODC) activity in a dose-dependent manner. Pretreatment of the cells with GTP was found to result in dose-dependent inhibition of colony formation in anchorage-independent growth assay of LNCaP cells. Prior treatment of the cells with GTP completely abolished the testosterone-mediated significant increase in the level of ODC mRNA (22).

ANIMAL STUDIES

We have shown, employing transgenic adenocarcinoma of the mouse prostate (TRAMP) mice, that oral infusion of GTP at a human achievable dose (equivalent to 6 cups of green tea/day) significantly inhibits PCa development and increases tumor free and overall survival of mice. GTP, provided as the sole source of drinking fluid to TRAMP mice from 8 to 32 wk of age, resulted in significant delay in primary tumor incidence and tumor burden as assessed sequentially by MRI, significant decrease in prostate and genitourinary weight; inhibition in serum insulin-like growth factor-I (IGF-1), and restoration of insulin-like growth factor binding protein-3 (IGFBP-3) levels and reduction in the protein expression of proliferating cell nuclear antigen (PCNA) in the prostate compared with water-fed TRAMP mice (23). The cellular DNA replication factor minichromosome maintenance protein (MCM)-7 has been implicated in PCa progression, growth, and invasion. Recently, it has been shown by DNA microarray, immunohistochemistry, and Western blot analysis that MCM-7 gene expression was reduced by GTC in TRAMP mice (24). Recently, we have demonstrated that continuous GTP infusion for 32 wk resulted in substantial reduction in expression of NFκB, IKKα, IKKβ, RANK, NIK, and STAT-3 in dorsolateral prostate of TRAMP mice. The level of transcription factor osteopontin was also downregulated, and there was shift in balance between Bax and Bcl2 favoring apoptosis in the dorsolateral prostate of TRAMP mice fed GTP (25). It has been reported that EGCG inhibited early but not late

Downloaded By: [University of Washington] At: 21:03 28 February 2010

stage PCa in the TRAMP mice. In the ventral prostate, EGCG significantly reduced cell proliferation, induced apoptosis, and decreased androgen receptor (AR), insulin-like growth factor-1 (IGF-1), IGF-1 receptor, phospho-ERK1/2, COX-2, and inducible nitric oxide synthase (iNOS) (26). In athymic nude mice implanted with androgen-sensitive CWR22Rυ1 cells, combination treatment with GTP and celecoxib resulted in enhanced tumor growth inhibition, lowering of prostate-specific antigen (PSA) levels, lowering of IGF-1 levels, and circulating levels of serum IGF-BP-3 compared with results of single-agent treatment (10). In athymic nude mice implanted CWR22Rυ1 cells, treatment with GTP, water extract of black tea, EGCG, and theaflavins resulted in significant inhibition in growth of implanted prostate tumors, reduction in the level of serum PSA, induction of apoptosis accompanied with upregulation in Bax and decrease in Bcl-2 proteins, and decrease in the levels of VEGF protein (27). In athymic nude mice implanted with human PCa PC-3 cells, diet containing lysine, proline, arginine, ascorbic acid, and green tea extract caused inhibition of tumor growth, inhibition of MMP-9, VEGF secretion, and mitosis in tissues (28). GTP feeding to TRAMP mice resulted in marked inhibition of PCa progression, which was associated with reduction of S100A4 and restoration of E-cadherin (29). Continuous GTP administration for 24 wk to TRAMP mice resulted in reduction in the levels of IGF-1 and increase in the levels of IGFBP-3 in the dorsolateral prostate with an inhibition of protein expression of PI3K, Akt, and ERK 1/2. There was also inhibition of VEGF, uPA, and MMP-2 and -9 (30). In TRAMP mice, treated with GTC, clusterin mRNA and protein progressively accumulated in the prostate gland. Upregulation of histone H3 and downregulation of growth arrest-specific gene 1 mRNAs in PCa-developing TRAMP mice demonstrated a high proliferation rate in tumors, whereas the opposite occurred in the glands of GTC-treated animals. Failure of GTC chemoprevention caused induction of both histone H3 and Gas1 and downregulation of clusterin. Immunohistochemistry experiments confirmed downregulation of clusterin during PCa onset and progression, and clusterin sustained expression in GTC treated TRAMP mice (31). In a mouse model of orthotopic androgen-sensitive human PCa, soy phytochemical concentrate (SPC), black tea, and green tea significantly reduced tumorigenicity. The combination of SPC and green tea synergistically inhibited final tumor weight and metastasis and significantly reduced serum concentrations of both testosterone and DHT in vivo. Inhibition of tumor progression was associated with reduced tumor cell proliferation and tumor angiogenesis (32). We earlier reported that oral feeding of GTP in drinking water for 7 days before testosterone administration resulted in decrease in testosterone-caused induction of ODC activity in sham-operated and castrated rats. Similar results were obtained with C57BL/6 mice in which testosterone treatment at similar dosage resulted in a twofold increase in ODC activity in the ventral prostate, and prior oral feeding with GTP resulted in inhibition of this induction (33).

TABLE 1
Reported effects of green tea in humans[a]

Effect of Green Tea in Humans	Reference
In a phase II trial, decrease in PSA in 2% of cohort, green tea toxicity in 69% of patients with androgen independent PCa	34
In patients of HRPCa, 9 had progressive disease within 2 months of starting therapy and 6 developed progressive disease after additional 1 to 4 months of therapy.	35
In the Japan Public Health Center-based Prospective Study, green tea consumption was associated with a dose-dependent decrease in the risk of advanced PCa	36
In HG-PIN volunteers, there was 3% tumor incidence in GTC-treated men as compared to 30% in placebo-treated men with no significant side-effects and lower urinary tract symptoms.	37
In a 2-yr follow-up, long-lasting inhibition of PCa progression was achieved after 1 yr of GTC administration; there was an almost 80% reduction in PCa diagnosis, from 53% to 11%, on treatment with GTC	38
In a case-control study conducted in southeast China in patients with histologically confirmed adenocarcinoma of the prostate, the PCa risk declined with increasing frequency, duration, and quantity of green tea consumption	40

[a] Abbreviations are as follows: PSA, prostate-specific antigen; PCa, prostate cancer; HRPCa, hormone refractory PCa; HG-PIN, high-grade prostate intraepithelial neoplasia; GTC, green tea catechins.

STUDIES IN HUMANS

The effects of green tea consumption in humans have been reported (Table 1). In a Phase II trial exploring green tea's antineoplastic effects in patients with androgen independent prostate carcinoma, 42 patients who were asymptomatic and had manifested, progressive PSA elevation with hormone therapy were evaluated. Patients were instructed to take 6 g of green tea per day orally in 6 divided doses and were monitored monthly for response and toxicity. Tumor response, defined as a decline in the baseline PSA value, occurred in a single patient or 2% of the cohort and was not sustained beyond 2 mo. The median change in the PSA value from baseline for the cohort increased by 43% at the end of the first month. Green tea toxicity, usually Grade 1 or 2, occurred in 69% of patients; however, 6 episodes of Grade 3 toxicity and one episode of Grade 4 toxicity also occurred. Thus, it was concluded that green tea carried limited antineoplastic activity, as defined by a decline in PSA levels, among patients with androgen independent prostate carcinoma (34). Efficacy of green tea, prescribed as an alternative complementary

Downloaded By: [University of Washington] At: 21:03 28 February 2010

formulation, was tested on hormone refractory prostate cancer (HRPCa). Patients with HRPCa were prescribed green tea capsules at 250 mg twice daily. Efficacy and toxicity were evaluated during monthly visits. The primary endpoint was PSA or measurable disease progression after a minimum of 2 mo of therapy. The treatment was generally well tolerated. Among 19 patients enrolled in the study, 12 patients reported at least one side effect, and only 2 of these were of moderate or severe grade. Four patients did not complete the minimum 2 mo of therapy, and 15 patients completed at least 2 mo of therapy. Of these patients, 9 had progressive disease within 2 mo of starting therapy, and 6 patients developed progressive disease after an additional 1 to 4 mo of therapy. It was concluded that green tea had minimal clinical activity against HRPCa (35).

In the Japan Public Health Center-based Prospective Study, 49,920 men aged 40 to 69 yr completed a questionnaire that included their green tea consumption habit. During this time, 404 men were newly diagnosed with prostate cancer, of which 114 had advanced cases, 271 were localized, and 19 were of an undetermined stage. Green tea was not associated with localized PCa. However, consumption was associated with a dose-dependent decrease in the risk of advanced PCa. The multivariate relative risk was 0.52 for men drinking 5 or more cups/day compared with less than 1 cup/day (36). A proof-of-principle clinical trial was conducted to assess the safety and efficacy of GTC for the chemoprevention of PCa in high-grade prostate intraepithelial neoplasia (HG-PIN) volunteers. Daily treatment consisted of 3 GTC capsules, 200 mg each. After 1 yr, only one tumor was diagnosed among the 30 GTCs-treated men with an incidence of 3%, whereas 9 cancers were found among the 30 placebo-treated men with an incidence of 30%. There was no significant change in total PSA between the two arms, but GTC-treated men showed values constantly lower with respect to placebo-treated ones. International Prostate Symptom Score and quality of life scores of GTCs-treated men with coexistent benign prostate hyperplasia (BPH) improved, reaching statistical significance in the case of International Prostate Symptom Scores. No reports of significant side effects were documented. Administration of GTC also reduced lower urinary tract symptoms, suggesting that GTC might also be of help for treating the symptoms of BPH (37). Another round of prostate mapping was done in a subset of these HG-PIN patients after a 2-yr follow-up. The mean follow-up from the end of GTC dosing was 23.3 mo for the placebo arm and 19.1 mo for the GTC arm. The third prostate mapping was done in only 9 from the placebo arm and 13 from the GTC arm. There was appearance of three further cancer diagnoses during follow-up, two in the placebo arm and one in the GTC arm. Long-lasting inhibition of PCa progression was achieved in these subjects after 1 yr of GTC administration. The treatment effect on early lesions suggested the early emergence of benefit observed at 6 mo. There was an almost 80% reduction in PCa diagnosis, from 53% to 11%, on treatment with GTC (38). Bettuzzi et al. (39) described and validated a RT-qPCR method based on an 8-genes signature that significantly discriminated benign tissue from PCa in both humans and TRAMP mice spontaneously developing PCa. The GTC-resistant PCa was significantly discriminated from GTC-sensitive PCa in the animal model. It has also been shown that this method can be successfully applied to a single tissue needle biopsy specimen in humans by preliminary experiments (39). A case-control study was conducted in Hangzhou, southeast China, and the cases were 130 incident patients with histologically confirmed adenocarcinoma of the prostate. The controls were 274 hospital inpatients without PCa or any other malignant diseases and matched to the age of cases. Face-to-face interviews were conducted using a structured questionnaire to gain information on duration, quantity, and frequency of usual tea consumption as well as the number of new batches brewed per day. The risk of prostate cancer for tea consumption was assessed using multivariate logistic regression adjusting for age, locality, education, income, body mass index, physical activity, alcohol consumption, tobacco smoking, total fat intake, marital status, age at marriage, number of children, and family history of PCa. The PCa risk declined with increasing frequency, duration, and quantity of green tea consumption; and the dose-response relationships were also significant, suggesting that green tea is protective against PCa (40).

CONCLUSION AND FUTURE PROSPECTS

The possible cancer-preventive activity of green tea constituents has been studied extensively. Various evidences from in vitro, in vivo, and clinical trials suggest that green tea and its constituents are effective in preventing PCa. The descriptive epidemiology of PCa suggests that it is a preventable disease. Prevention has the potential of saving lives and reducing the morbidity of radical PCa therapy. The development of chemoprevention strategies against PCa will have a huge impact both medically and economically. For example, if green tea consumption could be shown to retard emergence of BPH or androgen resistance, then it could prove to delay the onset of PCa. However, green tea is ineffective as a treatment, or an adjuvant treatment, for patients with PCa, especially hormone-independent PCa. Despite this, it appears from epidemiology and animal model studies that green tea does play a role in the prevention of PCa. It is important to develop strategies to strategically proceed for the design and selection of test agents to demonstrate clinical benefit with the minimum of adverse effects.

ACKNOWLEDGMENT

The original work from the author's (H. Mukhtar) laboratory outlined in this review was supported by United States Public Health Service Grants RO1 CA 78809, RO1 CA 101039, RO1 CA 120451, and P50 DK065303.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, et al.: Cancer statistics, 2009. *CA Cancer J Clin* **59,** 225–249, 2009.

Downloaded By: [University of Washington] At: 21:03 28 February 2010

2. Syed DN, Khan N, Afaq F, and Mukhtar H: Chemoprevention of prostate cancer through dietary agents: progress and promise. *Cancer Epidemiol Biomarkers Prev* **16,** 2193–2203, 2007.
3. Adhami VM and Mukhtar H: Polyphenols from green tea and pomegranate for prevention of prostate cancer. *Free Radic Res* **40,** 1095–1104, 2006.
4. Konishi N, Shimada K, Ishida E, and Nakamura M: Molecular pathology of prostate cancer. *Pathol Int* **55,** 531–539, 2005.
5. Mukhtar H and Ahmad N: Cancer chemoprevention: future holds in multiple agents. *Toxicol Appl Pharmacol* **158,** 207–210, 1999.
6. Khan N, Afaq F, and Mukhtar H: Cancer chemoprevention through dietary antioxidants: progress and promise. *Antioxid Redox Signal* **10,** 475–510, 2008.
7. Cao Y, Cao R, and Brakenhielm E: Antiangiogenic mechanisms of diet-derived polyphenols. *J Nutr Biochem* **13,** 380–390, 2002.
8. Khan N and Mukhtar H: Tea polyphenols for health promotion. *Life Sci* **81,** 519–533, 2007.
9. Ahmad N, Feyes DK, Nieminen AL, Agarwal R, and Mukhtar H: Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. *J Natl Cancer Inst* **89,** 1881–1886, 1997.
10. Adhami VM, Malik A, Zaman N, Sarfaraz S, Siddiqui IA, et al.: Combined inhibitory effects of green tea polyphenols and selective cyclooxygenase-2 inhibitors on the growth of human prostate cancer cells both in vitro and in vivo. *Clin Cancer Res* **13,** 1611–1619, 2007.
11. Siddiqui IA, Malik A, Adhami VM, Asim M, Hafeez BB, et al.: Green tea polyphenol EGCG sensitizes human prostate carcinoma LNCaP cells to TRAIL-mediated apoptosis and synergistically inhibits biomarkers associated with angiogenesis and metastasis. *Oncogene* **27,** 2055–2063, 2008.
12. Hastak K, Agarwal MK, Mukhtar H, and Agarwal ML: Ablation of either p21 or Bax prevents p53-dependent apoptosis induced by green tea polyphenol epigallocatechin-3-gallate. *FASEB J* **19,** 789–791, 2005.
13. Hussain T, Gupta S, Adhami VM, and Mukhtar H: Green tea constituent epigallocatechin-3-gallate selectively inhibits COX-2 without affecting COX-1 expression in human prostate carcinoma cells. *Int J Cancer* **113,** 660–669, 2005.
14. Pezzato E, Sartor L, Dell'Aica I, Dittadi R, Gion M, et al.: Prostate carcinoma and green tea: PSA-triggered basement membrane degradation and MMP-2 activation are inhibited by (-)epigallocatechin-3-gallate. *Int J Cancer* **112,** 787–792, 2004.
15. Siddiqui IA, Adhami VM, Afaq F, Ahmad N, and Mukhtar H: Modulation of phosphatidylinositol-3-kinase/protein kinase B- and mitogen-activated protein kinase-pathways by tea polyphenols in human prostate cancer cells. *J Cell Biochem* **91,** 232–242, 2004.
16. Brusselmans K, De Schrijver E, Heyns W, Verhoeven G, and Swinnen JV: Epigallocatechin-3-gallate is a potent natural inhibitor of fatty acid synthase in intact cells and selectively induces apoptosis in prostate cancer cells. *Int J Cancer* **106,** 856–862, 2003.
17. Hastak K, Gupta S, Ahmad N, Agarwal MK, Agarwal ML, et al.: Role of p53 and NF-kappaB in epigallocatechin-3-gallate-induced apoptosis of LNCaP cells. *Oncogene* **22,** 4851–4859, 2003.
18. Gupta S, Hussain T, and Mukhtar H: Molecular pathway for (−)-epigallocatechin-3-gallate-induced cell cycle arrest and apoptosis of human prostate carcinoma cells. *Arch Biochem Biophys* **410,** 177–185, 2003.
19. Nam S, Smith DM, and Dou QP: Ester bond-containing tea polyphenols potently inhibit proteasome activity in vitro and in vivo. *J Biol Chem* **276,** 13322–13330, 2001.
20. Chung LY, Cheung TC, Kong SK, Fung KP, Choy YM, et al.: Induction of apoptosis by green tea catechins in human prostate cancer DU145 cells. *Life Sci* **68,** 1207–1214, 2001.
21. Gupta S, Ahmad N, Nieminen AL, and Mukhtar H: Growth inhibition, cell-cycle dysregulation, and induction of apoptosis by green tea constituent (−)-epigallocatechin-3-gallate in androgen-sensitive and androgen-insensitive human prostate carcinoma cells. *Toxicol Appl Pharmacol* **164,** 82–90, 2000.
22. Gupta S, Ahmad N, Mohan RR, Husain MM, and Mukhtar H: Prostate cancer chemoprevention by green tea: in vitro and in vivo inhibition of testosterone-mediated induction of ornithine decarboxylase. *Cancer Res* **59,** 2115–2120, 1999.
23. Gupta S, Hastak K, Ahmad N, Lewin JS, and Mukhtar H: Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. *Proc Natl Acad Sci USA* **98,** 10350–10355, 2001.
24. McCarthy S, Caporali A, Enkemann S, Scaltriti M, Eschrich S, et al.: Green tea catechins suppress the DNA synthesis marker MCM7 in the TRAMP model of prostate cancer. *Mol Oncol* **1,** 196–204, 2007.
25. Siddiqui IA, Shukla Y, Adhami VM, Sarfaraz S, Asim M, et al.: Suppression of NFkappaB and its regulated gene products by oral administration of green tea polyphenols in an autochthonous mouse prostate cancer model. *Pharm Res* **25,** 2135–2142, 2008.
26. Harper CE, Patel BB, Wang J, Eltoum IA, and Lamartiniere CA: Epigallocatechin-3-Gallate suppresses early stage, but not late stage prostate cancer in TRAMP mice: mechanisms of action. *Prostate* **67,** 1576–1589, 2007.
27. Siddiqui IA, Zaman N, Aziz MH, Reagan-Shaw SR, Sarfaraz S, et al.: Inhibition of CWR22Rnu1 tumor growth and PSA secretion in athymic nude mice by green and black teas. *Carcinogenesis* **27,** 833–839, 2006.
28. Roomi MW, Ivanov V, Kalinovsky T, Niedzwiecki A, and Rath M: In vivo antitumor effect of ascorbic acid, lysine, proline and green tea extract on human prostate cancer PC-3 xenografts in nude mice: evaluation of tumor growth and immunohistochemistry. *In Vivo* **19,** 179–183, 2005.
29. Saleem M, Adhami VM, Ahmad N, Gupta S, and Mukhtar H: Prognostic significance of metastasis-associated protein S100A4 (Mts1) in prostate cancer progression and chemoprevention regimens in an autochthonous mouse model. *Clin Cancer Res* **11,** 147–153, 2005.
30. Adhami VM, Siddiqui IA, Ahmad N, Gupta S, and Mukhtar H: Oral consumption of green tea polyphenols inhibits insulin-like growth factor-I-induced signaling in an autochthonous mouse model of prostate cancer. *Cancer Res* **64,** 8715–8722, 2004.
31. Caporali A, Davalli P, Astancolle S, D'Arca D, Brausi M, et al.: The chemopreventive action of catechins in the TRAMP mouse model of prostate carcinogenesis is accompanied by clusterin over-expression. *Carcinogenesis* **25,** 2217–2224, 2004.
32. Zhou JR, Yu L, Zhong Y, and Blackburn GL: Soy phytochemicals and tea bioactive components synergistically inhibit androgen-sensitive human prostate tumors in mice. *J Nutr* **133,** 516–521, 2003.
33. Gupta S, Ahmad N, Mohan RR, Husain MM, and Mukhtar H: Prostate cancer chemoprevention by green tea: in vitro and in vivo inhibition of testosterone-mediated induction of ornithine decarboxylase. *Cancer Res* **59,** 2115–2120, 1999.
34. Jatoi A, Ellison N, Burch PA, Sloan JA, Dakhil SR, et al.: A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. *Cancer* **97,** 1442–1446, 2003.
35. Choan E, Segal R, Jonker D, Malone S, Reaume N, et al.: A prospective clinical trial of green tea for hormone refractory prostate cancer: an evaluation of the complementary/alternative therapy approach. *Urol Oncol* **23,** 108–113, 2005.
36. Kurahashi N, Sasazuki S, Iwasaki M, Inoue M, and Tsugane S: Green tea consumption and prostate cancer risk in Japanese men: a prospective study. *Am J Epidemiol* **167,** 71–77, 2008.
37. Bettuzzi S, Brausi M, Rizzi F, Castagnetti G, Peracchia G, et al.: Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study. *Cancer Res* **66,** 1234–1240, 2006.

38. Brausi M, Rizzi F, and Bettuzzi S: Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. *Eur Urol* **54,** 472–473, 2008.
39. Bettuzzi S, Rizzi F, and Belloni L: Clinical relevance of the inhibitory effect of green tea catechins (GtCs) on prostate cancer progression in combination with molecular profiling of catechin-resistant tumors: an integrated view. *Pol J Vet Sci* **10,** 57–60, 2007.
40. Jian L, Xie LP, Lee AH, and Binns CW: Protective effect of green tea against prostate cancer: a case-control study in southeast China. *Int J Cancer* **108,** 130–135, 2004.

Downloaded By: [University of Washington] At: 21:03 28 February 2010