Green Tea Polyphenols and Cancer Chemoprevention of Genitourinary Cancer

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OVERVIEW

Green tea, which has higher concentrations of polyphenols than other teas, has been correlated with reduced risk of various malignancies with most data supporting a potential protective role in prostate neoplasia. Preclinical studies over the last 25 years implicate constituent green tea catechins, epigallocatechin-3-gallate (EGCG) being the predominant form, as the main mechanistic ingredient in the observed biologic effects, which vary from proapoptotic effects to inhibition of androgen receptor and signal transduction pathways. There have been few prospective clinical trials of green tea polyphenols (GTP), especially with well-characterized formulations and doses. Although there have been hints of beneficial clinical activity in prostate neoplasia, other studies have raised concerns about the limited bioavailability and very low target-tissue concentrations of GTPs. At present there is no proven role for GTP supplementation in the prevention of genitourinary (GU) malignancies, but novel GTP formulations and further clinical testing may still support a future for GTP supplementation in GU cancer prevention.

The marked geographic/cultural differences and known migration shifts in the risk of prostate and bladder cancer strongly implicate an environmental role in their carcinogenesis.[1] Most of the focus of environmental exposure has been on dietary differences across and within world regions/cultures. One of the strongest dietary correlations with reduced risk of various malignancies has been tea ingestion, especially green tea, which originates from, and is predominantly consumed in, Asia and the Middle East.[2] Green tea, along with black and oolong tea, is derived from the plant species *Camellia sinensis,* but they differ in their handling and preparation of the tea leaves, with green tea resulting from the steaming of fresh leaves. This results in less oxidation of the main constituents (polyphenols) and thus, higher concentrations of polyphenols, as compared with the greater oxidation and thus, lower concentrations of polyphenols that occur in black and oolong tea. The steeping of green tea leaves in near boiling water releases into the liquid a rich collection of polyphenolic compounds (catechins, anthocyanins, phenolic acids), caffeine, theanine, tannins, trace elements, and vitamins.[3] One cup of green tea contains on average 100 mg of polyphenols and 50 mg of caffeine. The main green tea constituent polyphenols are catechins (flavanols) with the predominant and most studied catechin being epigallocatechin-3-gallate (EGCG) and lesser amounts of epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epicatechin (EC). The strong antioxidant and other purported intracellular and extracellular effects of green tea polyphenols (GTPs) along with many epidemiologic studies have led to the study of their preventive and therapeutic potential in many diseases and malignancies.

EPIDEMIOLOGY OF GREEN TEA POLYPHENOLS IN GU MALIGNANCIES

The relationship between green tea consumption and many different malignancies has been studied, and there are numerous reviews available.[2,3] The historic stark contrast in prostate cancer incidence between North America and some Asian countries has resulted in much of the epidemiologic focus on green tea and prostate cancer. Our review[3] found six published case-control or cohort studies, and a Cochrane Database review[2] that included four of the prior mentioned six studies. All studies evaluated quartiles or quintiles of green tea consumption (e.g., $<$ 1 cup/day, 1 to 2 cups/day, up to $>$ 5 cups/day) in populations (cohort studies of 25,000 to 90,000 patients; case control 130 to 140 patients) from Japan or China. Half the studies observed a significant ($p < 0.05$) risk reduction in prostate cancer incidence with increasing ingestion of green tea. With the exception of one study, even the negative studies reported a smaller, but not statistically significant, relative decreased risk with increasing green tea consumption. Not included in the above discussion is one cohort study with contrary findings[4] in which approximately 8,000 Hawaiians of Japanese ancestry underwent prospective analysis of demographics and diet and were observed to have

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a nonsignificant increased risk of developing prostate cancer with increased green tea consumption. Interestingly, this study also found an increased risk in patients who regularly consumed soy and tofu.

Epidemiologic studies assessing the relationship between green tea consumption and bladder cancer risk have been more limited and mainly characterized by numerous small case-control studies in Asia and a few large, well-controlled cohort studies.[5] A recent meta-analysis of published studies found no relationship between green tea consumption and bladder cancer risk.[5] A population-based case-control study in the United States examined tea consumption (they did not specify tea type) relative to risk of bladder and kidney cancer and observed a possible association between the highest tea consumption group (> 5 cups/day) and bladder cancer (overall risk 0.7; 95% CI 0.5, 1.0).[6] Overall the study could not find evidence of a dose-response relation between tea consumption and risk.

PRECLINICAL RESEARCH EXPLORING THE ANTICANCER EFFECTS OF GTPs

Some of the aforementioned epidemiology studies in the 1980s led to the preclinical study of green tea constituents by H. Mukhtar, initially in skin carcinogenesis models, followed shortly by animal modeling, and in vitro research in other neoplasia including prostatic.[7-10] Early research observed that a polyphenolic component of green tea was critical to its antitumor effects and these main polyphenolic constituents were the aforementioned catechins EGCG, EGC, ECG and EC.[9,11] EGCG, the most abundant and studied catechin, has significant in vitro growth-inhibitory properties in prostate cancer cells that vary with length of exposure as well as the cell line that was used.[12] A compelling observation was the marked differential toxicity between neoplastic and normal prostate cells; normal epithelial cells treated with EGCG have no observable toxicity at doses that are used for cancer inhibition studies.[8] As reviewed by us and others, there have been many observed extracellular and intracellular effects that might explain the observed inhibitory effects on uroepithelial carcinogenesis.[3,13] Some of the more prominent GTP effects that have been observed by multiple labs include proapoptotic effects and G_0/G_1 cell cycle arrest; inhibitory effects on NF-kB and COX-2 pathways of inflammation; decreased phosphorylation of MAP kinases, phosphoinositide 3-kinase, and protein kinase C; decreased tissue expression and decreased extracellular concentrations of insulin-like growth factor 1(IGF-1) with corresponding decreased IGF-1/insulin-like growth factor-binding protein 3 (IGFBP-3) ratio; and decreased androgen receptor expression.[3]

KEY POINTS

- The majority of epidemiologic studies have observed a correlation between increased green tea consumption and reduced risk of prostate cancer.
- Preclinical study of green tea constituents strongly implicate green tea catechins as the main purveyor of the multitude of observed intra- and extracellular effects, which might lead to beneficial health effects.
- The bioavailability of green tea polyphenols/catechins is relatively poor, and there has been no evidence of target-tissue accumulation.
- There have been very few well-controlled clinical trials of green tea polyphenols to date, but there has been evidence of potential beneficial effects for early prostate neoplasia in small, prospective trials.
- New formulations of natural products like green tea polyphenols may circumvent the poor bioavailability and lead to a greater benefit-risk ratio.

CLINICAL TRIALS OF GTP

Despite the wide-spread consumption of green tea, prospective clinical study is limited. A phase I dose-escalation study of an oral green tea extract (only 13% EGCG, but 7% caffeine) observed dose-limiting toxicities secondary to caffeine.[14] A dose of 1 g/m^2 three times daily (equivalent to eight Japanese cups of green tea three times a day) was recommended for future longer-term studies. Chow et al.[15,16] performed single- and multidose phase I comparative pharmacokinetic analyses of supplemental EGCG alone and polyphenon E (a proprietary formulation of green tea catechins), each formulated to contain 200 mg EGCG per capsule. They observed no difference in EGCG pharmacokinetics (free EGCG C_{max}—

TABLE 1. Glossary

Green tea	The liquid drink, made from steeping fresh (green) tea leaves from the *Camellia sinensis* plant, contains various polyphenols and caffeine.
Black tea	The liquid drink, made from steeping withered (black) tea leaves from the *Camellia sinensis* plant, contains various polyphenols (in smaller amounts than green tea) and caffeine.
Oolong tea	The liquid drink, made from steeping slightly withered tea leaves from the *Camellia sinensis* plant, contains various polyphenols (in slightly smaller amounts than green tea) and caffeine.
Green tea polyphenols	A mixture of the polyphenolic components (catechins, anthocyanins, phenolic acids) of green tea without caffeine but is often used interchangeably to mean the main green tea catechins.
Green tea catechins	A group of flavanols that are the most abundant polyphenols in green tea.
Green tea extract	A solid mixture of all the components of green tea including caffeine.
EGCG	Epigallocatechin-3-gallate, the predominant polyphenolic component of green tea and hypothesized to be the main contributor toward observed mechanistic effects.
Polyphenon E	Proprietary formulation of green tea catechins predominated by EGCG and dosed according to the amount of EGCG administered.

200 to 400 ng/mL, AUC—90 to 140 minutes-ug/mL; and half-life—2 hours) between the two formulations, no accumulation of EGCG after multiple doses, and no difference in adverse events between the patients taking the placebo and those taking the GTP. These data confirm the relatively poor oral bioavailability and high interpatient variability in EGCG pharmacokinetics. EGCG undergoes extensive biotransformation to methylated, sulfated, and glucuronidated forms through the action of enzymes including liver cytosolic UDP-glucuronsyl transferase, sulfotransferase, and catechol-O-methyltransferase (COMT).[17] Functional polymorphisms in these enzymes may contribute to some of the observed variability in pharmacokinetics.

Early clinical trials of GTP in prostate cancer were characterized by single-arm studies in patients with advanced disease with no accompanying mechanistic studies and uncertain formulations of GTP. In a study by Jatoi et al.[18] patients with castration-resistant advanced prostate cancer were administered 6 g of green tea daily. Although the safety of green tea was confirmed in these patients, no clinical benefit was observed. Similarly, Choan et al.[19] found that administration of green tea extract (250 mg twice daily) resulted in no patients having a PSA decline greater than 50% from baseline, although six of the 15 patients demonstrated slowing of PSA progression lasting 1 to 4 months. These relatively negative results need to be interpreted relative to the advanced disease status of the patients, the uncertainties of the formulations, and the delivery of relatively small amounts of EGCG or other catechins ($<$ 400 mg/day).

More recent studies of GTP in prostate cancer have used formulations with standard, reproducible amounts of catechins and more controlled trial designs. Because high-grade prostatic intraepithelial neoplasia is closely linked to prostate cancer and may be a precursor lesion, Bettuzi et al. studied GTP in this population.[20] They performed a randomized, double-blinded, placebo-controlled trial of GTP (EGCG 600 mg, EGC, EC) daily for 1 year in 60 men with high-grade prostatic intraepithelial neoplasia. Prostate biopsies done after 6 and 12 months on study observed nine of 30 patients administered the placebo with progression to prostate cancer as compared with one of 30 patients given GTP. Additional years of follow-up continued to show a decreased progression to prostate cancer in patients assigned GTP.[21] GTP was tolerated well with no increased toxicity as compared with the placebo, illustrating the safety of long-term administration of GTP along with the aforementioned signs of potential biologic activity in prostate neoplasia.

Recently McLarty et al. published the results of a single-arm study of 26 men who were given GTP (800 mg EGCG once a day) for 12 to 214 (median 35) days before prostatectomy for early-stage prostate cancer.[22] Comparing patients' values from baseline to day of surgery revealed a significant reduction in multiple biomarkers including serum PSA, IGF-1, IGF-1/IGF-BP3 ratio, hepatocyte growth factor and vascular endothelial growth factor (VEGF). Eighteen of the 26 patients had their serum PSA decrease after taking EGCG, and the longer a patient took GTP the more likely there was to be a decrease in PSA. Of the 18 patients with a decrease in serum PSA, 10 patients had a decline of 20% or more over the course of the study. Not surprisingly, reductions in IGF-1/IGF-BP3, VEGF, and hepatocyte growth factor corresponded with PSA reduction in 14 of these 18 patients, and those patients with the greatest reduction in PSA appeared to have the greatest reduction in IGF-1 and VEGF. They also observed good tolerance with minimal to no signs of toxicity at 800 mg (EGCG dose) daily. Because it was not a blinded, placebo-controlled study, the results need to be interpreted cautiously.

Researchers at the University of Arizona evaluated the systemic and prostate-tissue effects of polyphenon E (800 mg EGCG) or a placebo daily for 3 to 6 weeks preceding a planned prostatectomy for early-stage prostate cancer in 48 men (mean age 63, mean serum PSA 6.7 $\pm$ 4 with 70% with Gleason 3+3) in a randomized, double-blinded trial.[23] There was no difference in toxicity between polyphenon E and the placebo with 18 and 39 adverse events respectively, but there was one patient given polyphenon E with grade 1 increase in serum alanine transaminase. Plasma EGCG concentrations sampled 12 to 24 hours after the last dose averaged 150 pmol/L. Five of 15 patients administered polyphenon E had detectable concentrations of EGC (18 to 60 pmol/g) in prostate tissue recovered at surgery done 24 or more hours after the last dose. Only one patient administered polyphenon E had detectable concentrations of EGCG, EC, or ECG in prostate tissue. Two of 19 patients assigned the placebo also had detectable concentrations of EGC in their prostate tissue at surgery. They noted minimal histologic changes in prostate neoplasia between the groups. There were nonsignificant trends toward decreased serum IGF-1, IGF-1/IGFBP-3 ratios, and decreased leukocyte DNA 8-dydroxy-2-deoxyguanosine/2-deoxyguanosine ratios in patients given polyphenon E from pre- to poststudy drug as compared with the patients assigned the placebo. The lack of significant concentrations of green tea catechins within the prostate tissue after 3 to 6 weeks of daily EGCG at 800 mg is potentially concerning.

There has been minimal clinical assessment of GTPs in bladder cancer whether as a preventive or therapy. Recently we performed a presurgical study of polyphenon E administered before trans-urethral resection of a bladder tumor for suspected superficial bladder cancer (Bailey, unpublished) similar to the aforementioned study by Nguyen in prostate cancer.[23] In a randomized, double-blind trial, 31 men and women were administered a placebo, 800, or 1,200 mg of EGCG (polyphenon E) daily for 2 to 4 weeks preceding a planned trans-urethral resection of a bladder tumor. Preliminary assessment of the recently completed study revealed no evidence of increased toxicity (adverse events) in the two treatment arms as compared with the placebo and assessment of uroepithelial green tea catechin concentrations is underway.

OTHER INDICATIONS/USES OF GTPs

GTPs have been studied more extensively in other disease states, especially cardiovascular and metabolic diseases. There have been prospective, controlled studies that have observed evidence of GTPs inducing beneficial metabolic effects (altered insulin resistance to slight weight loss), and similar studies have observed mixed results related to direct vascular effects of GTPs.[24] Additional observations relative to cancer and GTPs that are pertinent to the oncologist include recent data describing objective therapeutic efficacy of high-dose (>2,000 mg/day of EGCG) GTPs in chronic lymphocytic leukemia.[25] Shanafelt et al. administered polyphenon E (EGCG 2,000 mg twice daily) to 42 patients with stage zero to II chronic lymphocytic leukemia and observed more than 20% of the patients had transient improvement in leukocytosis and 69% had objective evidence of benefit in terms of improved adenopathy and/or biologic markers of disease. Besides the potential effectiveness, it is important to note the relative common occurrence of transient increases in serum hepatic transaminase levels (45% with grade 1 to 2 increases in aspartate aminotransferase or alanine transaminase) while taking increased dose of GTPs. Whether this could be a concern with larger populations at lower doses is yet to be determined.

NEW FORMULATIONS OF GTPs

A common issue with the application of most nutrient-derived novel anticancer agents has been poor bioavailability. The concentration of the green tea catechins observed in human studies has routinely been lower than that associated with many of the in vitro studies. Studies examining tissue concentrations of green tea catechins have observed low to undetectable levels without evidence of tissue accumulation over a few weeks of daily administration.[23] Therefore researchers are applying new formulation technologies to natural products like GTPs.[26] Currently multiple researchers are applying forms of encapsulation to natural products using liposomes, biodegradable polymers, dendrimers, and virus and magnetic nanoparticles.[26] An example of this is the Mukhtar laboratory's examination of GTP nanoformulations.[27] They tested EGCG loaded in polylactic acid-polyethylene glycol nanoparticles against human prostate cancer cells, under in vitro and in vivo conditions. They observed encapsulated EGCG retained its biologic effectiveness with over 10-fold dose advantage over nonencapsulated EGCG for exerting proapoptotic and angiogenesis inhibitory effects. This study constitutes evidence the effective chemopreventive concentration of EGCG in both in vitro and in vivo systems, could be lowered by nanoformulation.[27] Multiple other approaches for encapsulation of GTP/EGCG (bovine serum albumin nanoparticles, carbohydrate matrix of gum Arabic and maltrodextrin, radioactive gold nanoparticles, and diblock copolymer of polyactic co-glycolic acid-polyethylene glycol [-COOH]) are being pursued by investigators.[28] Given the effective use of novel encapsulation formulations in cancer therapeutics there may be significant promise for "nanochemoprevention" approaches to improve target tissue pharmacokinetics without increased toxicity.

FUTURE OF GTPs IN THE PREVENTION OF PROSTATE AND BLADDER CANCER

In many respects, the area of cancer chemoprevention starts with medical dictum "do no harm" or safety, followed later by effectiveness at decreasing the development of clinically significant cancers. This ratio of safety/effectiveness will likely be viewed differently as we continue to improve our ability to predict populations' and eventually individual's risk of clinically significant cancers. The ancient history of and evidence of the growing popularity of green tea ingestion suggests safety and, to some extent, health benefits. The limited clinical trials experience with green tea derivatives suggests that drinking large amounts of tea or ingesting green tea extracts containing substantial amounts of caffeine can and will induce side effects consistent with increased caffeine ingestion. Green tea products that contain predominantly GTPs with negligible amounts of caffeine are better tolerated, but at higher doses (≥ 2,000 mg EGCG per day) do have side effects like gastrointestinal upset and transient elevations in hepatic transaminases. For these reasons the recommended EGCG dose for cancer chemoprevention studies has been 800 mg daily.

Despite a growing amount of preclinical data observing desirable biologic effects of GTPs and the existence of numerous, supportive epidemiologic studies for health benefits of GTPs, prospective clinical trials evidence is limited. In the authors' opinion, this should be viewed as more related to the relatively few clinical trials performed rather than a biologically ineffective agent. There is more evidence to support the potential benefits of GTPs in prostate cancer prevention than uroepithelial cancer prevention at this point. Issues that should be addressed while assessing GTPs potential to prevent GU malignancies include whether bioavailability and/or tissue delivery matter, and if so, can this be overcome with novel formulations like nanoparticle delivery; our research and others suggest that GTPs' effects vary depending on where in the neoplastic process it is included (e.g., "it is much easier to move the stream at its beginning rather than when it is a river"); and can sufficiently large but economical prospective studies be performed to discern its value in cancer prevention when segments of the population and funding agencies have already decided natural products must work or they will never work as preventive agents.

Because the clinical research question "does GTP ingestion lead to a decreased incidence of prostate or bladder cancer" has yet to be asked in a randomized, prospective clinical trial in the United States or a comparable population, there is no clinical data to recommend GTPs as agents for the prevention of GU malignancies at this time. However, the existing epidemiologic and preclinical research data lead us and other researchers to continue studying its role in cancer prevention.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References

1. Trottier G, Boström PJ, Lawrentschuck N, et al. Nutraceuticals and prostate cancer prevention: a current review. *Nature Rev Urol.* 2010;7: 21-30.
2. Boehm K, Borrelli F, Ernst E, et al. Green tea (Camellia sinensis) for the prevention of cancer. *Cochrane Database Syst Rev.* 2009; 3:CD005004.
3. Johnson JJ, Bailey HH, Mukhtar H. Green tea polyphenols for prostate cancer chemoprevention: a translational perspective. *Phytomedicine.* 2010;17:3-13.
4. Severson RK, Nomura AM, Grove JS, et al. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. *Cancer Res.* 1989;49:1857-1860.
5. Wu S, Li F, Huang X, et al. The association of tea consumption with bladder cancer risk: a meta-analysis. *Asia Pac J Clin Nutr.* 2013;22:128-137.
6. Bianchi GD, Cerhan JR, Parker AS, et al. Tea consumption and risk of bladder and kidney cancers in a population-based case-control study. *Am J Epidemiol.* 2000;151:377-383.
7. Wang ZY, Khan WA, Bickers DR, et al. Protection against polycyclic aromatic hydrocarbon-induced skin tumor initiation in mice by green tea polyphenols. *Carcinogenesis.* 1989;10:411-415.
8. Ahmad N, Feyes DK, Nieminen AL, et al. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. *J Natl Cancer Inst.* 1997;89:1881-1886.
9. Katiyar SK, Agarwal R, Wang ZY, et al. (-)-Epigallocatechin-3-gallate in Camellia sinensis leaves from Himalayan region of Sikkim: inhibitory effects against biochemical events and tumor initiation in Sencar mouse skin. *Nutr Cancer.* 1992;18:73-83.
10. Yang CS, Wang ZY. Tea and cancer. *J Natl Cancer Inst.* 1993;85:1038-1049.
11. Khan SG, Katiyar SK, Agarwal R, et al. Enhancement of antioxidant and phase II enzymes by oral feeding of green tea polyphenols in drinking water to SKH-1 hairless mice: possible role in cancer chemoprevention. *Cancer Res.* 1992;52:4050-4052.
12. Kweon MH, Adhami VM, Lee JS, et al. Constitutive overexpression of Nrf2-dependent heme oxygenase-1 in A549 cells contributes to resistance to apoptosis induced by epigallocatechin 3-gallate. *J Biol Chem.* 2006;281:33761-33772.
13. Yang CS, Wang H, Li GX, et al. Cancer prevention by tea: Evidence from laboratory studies. *Pharmacological Research.* 2011;64:113-122
14. Pisters KM, Newman RA, Coldman B, et al. Phase I trial of oral green tea extract in adult patients with solid tumors. *J Clin Oncol.* 2001;19:1830-1838.
15. Chow HH, Cai Y, Alberts DS, et al. Phase I pharmacokinetic study of tea polyphenols following single-dose administration of epigallocatechin gallate and polyphenon E. *Cancer Epidemiol Biomarkers Prev.* 2001;10: 53-58.
16. Chow HH, Cai Y, Hakim IA, et al. Pharmacokinetics and safety of green tea polyphenols after multiple-dose administration of epigallocatechin gallate and polyphenon E in healthy individuals. *Clin Cancer Res.* 2003; 9:3312-3319.
17. Moyers SB, Kumar NB. Green tea polyphenols and cancer chemoprevention: multiple mechanisms and endpoints for phase II trials. *Nutrition Reviews.* 2004;62:204-211.
18. Jatoi A, Ellison N, Burch PA, et al. A phase II trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. *Cancer.* 2003;97:1442-1446.
19. Choan E, Segal R, Jonker D, et al. A prospective clinical trial of green tea for hormone refractory prostate cancer: an evaluation of the complementary/alternative therapy approach. *Urol Oncol.* 2005;23:108-113.
20. Bettuzzi S, Brausi M, Rizzi F, 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.* 2006;66:1234-1240.
21. Brausi M, Rizzi F, Bettuzzi S. Chemoprevention of human prostate cancer by green tea catechins: two years later. A follow-up update. *Eur Urol.* 2008;54:472-473.
22. McLarty J, Bigelow RLH, Smith M, et al. Tea polyphenols decrease serum levels of prostate-specific antigen, hepatocyte growth factor, and vascular endothelial growth factor in prostate cancer patients and inhibit production of hepatocyte growth factor and vascular endothelial growth factor in vitro. *Cancer Prev Res (Phila).* 2009;2:673-682.
23. Nguyen MM, Ahmann FR, Nagle RB, et al. Randomized, double-blind, placebo-controlled trial of polyphenon E in prostate cancer patients before prostatectomy: Evaluation of potential chemopreventive activities. *Cancer Prev Res (Phila).* 2012;5:290-298.
24. Johnson R, Bryant S, Huntley AL. Green tea and green tea catechin extracts: an overview of the clinical evidence. *Maturitas.* 2012;73:280-287.
25. Shanafelt TD, Call TG, Zent CS, et al. Phase 2 trial of daily, oral Polyphenon E in patients with asymptomatic, Rai stage 0 to II chronic lymphocytic leukemia. *Cancer.* 2013;119:363-370.
26. Nair HB, Sung B, Yadav VR, et al. Delivery of antiinflammatory nutraceuticals by nanoparticles for the prevention and treatment of cancer. *Biochemical Pharmacology.* 2010;80:1833-1843.
27. Siddiqui IA, Adhami VM, Bharali DJ, et al. Introducing nanochemoprevention as a novel approach for cancer control: proof of principle with green tea polyphenol epigallocatechin-3-gallate. *Cancer Res.* 2009; 69:1712-1716.
28. Sanna V, Siddiqui IA, Sechi M, et al. Nanoformulation of natural products for prevention and therapy of prostate cancer. *Cancer Lett.* 2012 Epub 2012 Nov 29.