Tea Polyphenols and Theaflavins Are Present in Prostate Tissue of Humans and Mice after Green and Black Tea Consumption[1,2]

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ABSTRACT Green and black tea have shown promise in the chemoprevention of prostate cancer. The objective of this study was to determine the bioavailability and bioactivity of tea polyphenols (PP) and theaflavins in human serum and human and mouse tissues. A decaffeinated black tea diet was administered to C57BL/6 mice. PPs and theaflavins were found in the small and large intestine, liver, and prostate in conjugated and free forms. The relative prostate bioavailability of theaflavin was 70% higher than that of epigallocatechin gallate (EGCG). In the second mouse study, a green tea (GT) diet was administered followed by the control diet for 1–5 d. Epicatechin (EC), EGCG, and epicatechin gallate (ECG) concentrations in prostate tissue were significantly decreased after 1 d of consuming the control diet. Epigallocatechin gallate (EGC), however, did not decrease significantly. For the human study, 20 men scheduled for surgical prostatectomy were randomly assigned to consume 1.42 L daily of GT, BT, or a caffeine-matched soda control (SC) for 5 d before radical prostatectomy. Tea PPs were greater in prostate samples from men consuming BT and GT than in men consuming SC ($P = 0.0025$). Although tea PP were not detectable in serum, ex vivo LNCaP prostate cancer cell proliferation was less when cells were grown in media containing patient serum collected after BT ($P < 0.001$) and GT ($P = 0.025$) consumption relative to baseline serum This is the first human study to show that tea polyphenols and theaflavins are bioavailable in the prostate where they may be active in the prevention of prostate cancer. J. Nutr. 136: 1839–1843, 2006.

KEY WORDS: • *tea polyphenols* • *theaflavins* • *prostate cancer* • *ex vivo LNCaP bioassay*

Prostate cancer is a major public health concern and a leading cause of cancer-related deaths among men in the United States. (1). Chemoprevention involving the use of natural, nontoxic agents to prevent the process of carcinogenesis or its progression could be an effective approach to reduce the incidence and mortality of prostate cancer. A recent survey showed that >25% of patients with prostate carcinoma resort to nonprescription (so-called alternative) therapies including green tea and green tea extracts (2). Green and black tea, derived from the plant *Camellia sinensis*, are widely consumed throughout the world. Green tea (GT)[4] is manufactured by drying the leaves of *C. sinensis*, whereas the process of black tea (BT) manufacture requires an additional fermentation step. Fermenting the tea leaves mediates the oxidation of tea flavanols by polyphenoloxidase and generates the theaflavins and thearubigins found in BT (3). Theaflavins and thearubigins are oligomeric polyphenolic compounds synthesized from monomeric tea flavanol units (**Fig. 1**). Recent laboratory and epidemiological studies suggest that increased consumption of GT may prevent the development and progression of carcinoma of the prostate (4–7). Epidemiological data for the chemopreventive effect of BT are less convincing. This may be due to the lack of detailed information about type and preparation

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[4] Abbreviations used: BT, black tea; BW, body weight; EC, (-)-epicatechin; ECG, (-)-epicatechin gallate; EGC, (-)-epigallocatechin; EGCG, (-)-epigallocatechin gallate; FBS, fetal bovine serum; GT, green tea; HPLC-ECD, HPLC-electrochemical detection; LC-ESI-MS, LC-electrospray ionization-MS; PolyE, polyphenon E; PP, polyphenol; SC, soda control; THE, theaflavin; THE3G, theaflavin-3-gallate; THE3′G, theaflavin-3′-gallate; THE33′GG, theaflavin-3,3′-digallate.

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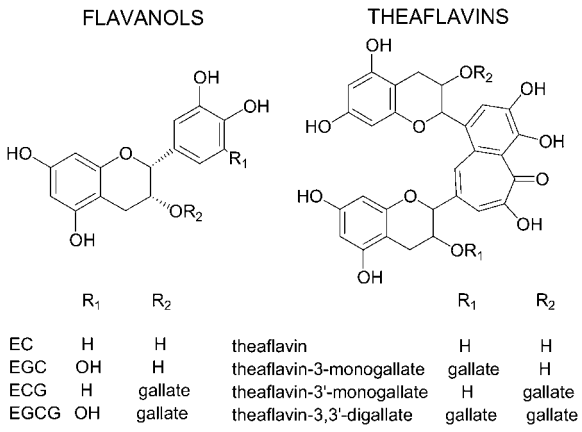

FIGURE 1 Chemical structures of tea flavanols and theaflavins.

method of the tea (8). The chemopreventive effects of tea have been attributed to the biochemical activities of its polyphenolic constituents such as (-)-epicatechin gallate (ECG), (-)-epicatechin (EC), (-)-epigallocatechin 3-gallate (EGCG), and (-)-epigallocatechin (EGC) (9). Despite increased interest in the possible preventive effects of tea polyphenols, information on the absorption, distribution, metabolism, and elimination of tea polyphenols (PP) in humans has not reflected the growing interest (10). Human pharmacokinetic studies provided information on the plasma concentration and urinary excretion of tea PP (11). In a rat study, EGC, EC, and EGCG were found in prostate and other tissues after chronic consumption of 0.6% green tea PPs in drinking water (12). To our knowledge, however, no data on the tissue bioavailability of BT PP in animals or the tissue bioavailability of GT or BT in humans are available.

SUBJECTS AND METHODS

Tea solids. Black tea solids were prepared in our laboratory by brewing Twinings English Breakfast tea (25 g tea/L boiling water). The tea was filtered (Whatman No.1 filter), followed by evaporation of the clear liquid using Rotavapor R-114 and the freeze-dry system Lyphlock 6 (Labconco). Caffeine was extracted from the tea brew using an equal volume of chloroform. The water phase was evaporated as described above for the production of black tea solids. The green tea extract Polyphenon E (PolyE) was generously provided by the Food Research Laboratories, Mitsui Nori. Poly E contains 71% EGCG, 7.8% EGC, 14% EC, and 7.2% ECG.

Mouse study. C57BL/6 mice were derived from our breeding colony; at ~6 wk of age, they were fed the decafBT-diet (50 mg/g AIN93G diet, Dyets) or GT-diet (20 mg/g AIN93G diet) for 2 wk (13). The PP content of the diets was analyzed by HPLC (**Table 1**). Although we confirmed that PPs in the diet were stable for 3 d, we provided fresh diet daily. Mice consumed a mean of 6.6 g/d. Animal protocols were approved by the University of California, Los Angeles Chancellor's Animal Care and Use Committee in accordance with the NIH guidelines. To determine the transit time of PP in prostate, mice were fed the GT-diet for 2 wk followed by 1–5 d of control AIN93G diet. All mice were killed between 1000 and 1200 h.

Human study. Men ($n = 20$) scheduled for radical prostatectomy, aged 54 to 76 y, were recruited at the VA Greater Los Angeles Healthcare System (VAGLAHS). The study was approved by both the VAGLAHS and the UCLA Institutional Review Boards. Informed consent was obtained from all subjects.

Study design. Participants were randomly assigned to the GT ($n = 8$), BT ($n = 7$), or the soda control (SC) group ($n = 5$). All study participants were asked to refrain from drinking any tea or tea-related beverages for 7 d before the start of study intervention. Participants were instructed to follow their usual diet before and during the intervention. At the baseline visit, a serum and urine sample was collected from each participant. Participants were provided with 25 tea bags or catechin-free soft drinks (regular or diet cola). The caffeine and tea polyphenol contents of the sodas and teas were determined in our laboratory (**Table 2**). Sodas were chosen to match the caffeine content of the tea intervention. Bigelow Darjeeling BT and Uncle Lee's GT were chosen based on the similarity in EGCG content. Participants were instructed on tea preparation and told to consume 284 mL 5 times spread throughout the day for 5 d starting 6 d before their scheduled surgery. On d 5 of tea consumption, participants continued the tea consumption and consumed their last cup of tea just before midnight on the night before surgery. On the day of surgery, a serum sample was obtained before the surgery. Immediately after surgical removal of the prostate, prostate tissue aliquots were removed by the pathologist and frozen as described below.

TABLE 1

Concentration of polyphenols and theaflavins in decaffeinated BT solids and BT and GT-diets used in the C57BL/6 mouse studies[1]

Polyphenol	DecafBT Solids	GT-diet	BT-diet
	mg/g tea solids	*mg/g diet*	
EGC	75.7 ± 0.54	0.56 ± 0.04	2.59 ± 0.04
EC	7.2 ± 0.05	1.51 ± 0.03	0.29 ± 0.001
EGCG	6.9 ± 0.04	6.51 ± 0.18	0.29 ± 0.01
ECG	12.5 ± 0.06	0.74 ± 0.01	0.47 ± 0.01
THE	14.4 ± 0.1	—[2]	0.65 ± 0.04
THE3G	19.0 ± 0.5	—[2]	0.95 ± 0.07
THE3′G	4.3 ± 0.1	—[2]	0.23 ± 0.03
THE33′GG	12.8 ± 0.6	—[2]	0.78 ± 0.08

[1] Values are means ± SD, $n = 2$.
[2] Below the detection limit of 0.01 mg/g diet.

Sample processing. Serum samples were frozen at −80°C in aliquots of 1 mL. Aliquots for HPLC flavanol analysis were protected from oxidation by the addition of 100 μL of 20% ascorbic acid-0.1% EDTA solution (0.4 mmol/L NaH_2PO_4, pH 3.6). Prostate tissue samples were frozen immediately in a mixture of methylbutane and dry ice and transferred to the −80°C freezer for storage until analysis.

Chemicals and reagents. EGCG, EGC, EC, ECG, β-D-glucuronidase type X-A from *Escherichia coli* and arylsulfatase type VIII from abalone entrails, dithionite, and black tea extract (mixture of theaflavins) were purchased from Sigma-Aldrich. GT bags (Uncle Lee's Tea®) and BT bags (Bigelow Darjeeling Blend, R.C. Bigelow) from one production lot were generously provided by the manufacturers. HPLC-grade acetonitrile, citric acid, and ammonium acetate were purchased from Fisher Scientific. Dansyl chloride (5-dimethylaminonaphthalene-1sulfonyl

TABLE 2

Concentration of tea polyphenols, theaflavins and caffeine in BT, GT and soda used in the human intervention[1]

Compound	BT[2]	GT	Soda
	mg/236 mL of brewed tea		*mg/236 mL*
EGC	25.8 ± 0.2	90.6 ± 0.3	—[3]
EC	9.9 ± 0.1	25.5 ± 0.09	—[3]
EGCG	57.7 ± 0.1	71.2 ± 1.1	—[3]
ECG	30.6 ± 0.3	39.8 ± 1.4	—[3]
Total theaflavins	8.8 + 0.2	—[3]	—[3]
Caffeine	67.2 ± 0.5	36.9 ± 0.2	26.5 ± 0.1
Total flavanol	124.1 ± 0.8	227.0 ± 2.1	—[3]

[1] Values are means ± SD, $n = 2$.
[2] Teas were prepared by adding 1 tea bag to 236 mL of boiling water for 5 min.
[3] Below the detection limit of 0.02 mg/236 mL.

chloride), 1,6-diaminohexane and sodium carbonate were purchased from Sigma-Aldrich. 7,3′,4′,5′-Tetrahydroxyflavone was purchased from Indofine Chemica. Theaflavins were purchased from Wako.

Analysis of tea polyphenols in tea and diet. The analysis of tea was performed as described previously (14).

Analysis of tea polyphenols in serum, tissue, and urine with HPLC-coulometric array ECD and LC-ESI-MS. PPs and theaflavins were extracted from animal and human tissue using a methanol:ethylacetate:dithionite (2:1:3) mixture during homogenization of the animal tissues following the method of Chu et al. (15). After evaporation of the organic solvents, extracts were treated with β-glucuronidase and aryl-sulfatase and extracted again. Combined extracts were analyzed using HPLC-electrochemical detection (ECD) (16). Human serum PP analysis was performed as described previously (16). Recovery of flavanols from plasma was determined in 3 different concentrations with each batch of plasma samples (95–105%). The detection limit was 0.02 μmol/L. LC-ESI-MS analysis was performed according to Li et al. (17) with minor modifications. A Thermo Finnigan LCQ Advantage ion trap MS with ESI source was used. Flavanols were separated using a C18 Symmetry column (Waters), 2.1 $\times$ 100 mm, and isocratic separation with a mobile phase of 15% acetonitrile in water containing 0.5% acetic acid. Samples were extracted the same way as for electrochemical detection with 7,3′,4′,5′-tetrahydroxyflavone as the internal standard. The LCQ ion trap mass detector was in negative ion polarity mode. The capillary temperature was 275°C, sheath gas and auxiliary gas were 40 and 0 L/min respectively, and source voltage was 4 kV. The collision energy was 40–45eV.

In vitro cell culture bioassay. LNCaP cells from the American Type Culture Collection were grown in 75-cm^2 flasks (Falcon) in RPMI-1640 medium without phenol red, supplemented with 10% fetal bovine serum (FBS), 10^5 IU/L penicillin, 200 μg/L streptomycin, and 4 nmol/L L-glutamine (Omega Scientific). The cultures were maintained in a humidified incubator (37°C, 5% CO_2) and passaged routinely at 80% confluence. Cells used in experiments were not passaged >10 times. Cells were detached with 0.25% trypsin-EDTA solution (Sigma Chemical), centrifuged at 500 $\times$ g, and resuspended in fresh medium. Cell viability was assessed via trypan blue exclusion. Cells were plated at 5 $\times$ 10^3 cells/well in 96-well plates, with all assays performed in triplicate. After 24 h, fresh medium with 10% FBS or 10% study participant serum was added to the wells and incubated for another 48 h. FBS was used as a control for each assay and LNCaP cell growth in media containing human serum was expressed as a percentage of LNCaP growth in media containing FBS. Cell growth was determined by the MTS Assay (Promega) as described previously (18).

Statistical methods. Total polyphenol concentrations in mouse tissue were compared with free polyphenol concentrations using a paired Student's t test for liver, small intestine, and colon (Prism4, GraphPad). Differences were considered significant at $P < 0.05$. For comparison of total vs. free polyphenol concentrations in mouse prostate, a non-paired Student's t test was used the small size of the mouse prostate made it necessary to use different mice. Prostate total polyphenol concentrations after feeding the control diet for 1–5 d were compared with d 0 concentrations using ANOVA (Prism4, GraphPad). The human study was a parallel 3-arm study. Eligible patients were randomly assigned to 1 of the 3 treatment groups: GT, BT, or SC. The major outcomes were tissue tea polyphenol concentration and ex vivo cell culture bioassay. Due to the small sample size, the nonparametric Kruskal-Wallis test was used to compare the 3 groups. If significant, pair-wise comparisons were carried out using the Wilcoxon rank sum test. Race was included in the original model, but was excluded from the final model because it did not significantly affect the outcome. To evaluate the data from the ex vivo cell culture bioassay, a mixed model was developed to evaluate the differences among the 3 groups and the difference before and after surgery within each group. The final model was: $Y_{ijtk} = \alpha + \tau_j + \gamma_t + (\tau\gamma)_{jt} + \beta_i + \varepsilon_{ijtk}$ where Y_{ijtk} is the k^{th} measurement for subject I (1,2,. . .n) in group j (1–3), at time t (1,2), τ_j and γ_t are the group and time (pre- and postsurgery) effects, respectively. $(\tau\gamma)_{jt}$ is the group by time interaction, β_i is a random subject effect, $\beta \sim N(0, G)$. The G matrix is the block diagonal with blocks corresponding to the subjects, each block having the compound-symmetry structure. ε_{ijtk} is the error term, $\varepsilon_{ijtk} \sim$ iid N $(0, \sigma^2)$. Statistical analysis software SAS version 8 was used to carry out the analyses.

RESULTS

Animal studies. The black tea was selected based on its high EGCG and theaflavin content. During the decaffeination process, however, the EGCG content decreased by 90%. After mixing the decafBT powder into the diet, the EGCG content was further decreased by 16% (Table 1). Based on the tissue concentrations, tea polyphenols and theaflavins were taken up into the small and large intestinal tissue, liver, and prostate (**Fig. 2**). The relative absorption (ratio of tissue concentration to total daily intake) of theaflavin into the prostate tissue was 70% greater than that of EGCG. In the small intestine, liver, and prostate, EGCG and ECG were present to a greater extent in the conjugated form, whereas prostate THE and THE3G were 50–100% in the free form (Fig. 2). EC and EGC were mainly in the free form. THE3′G and THE33'GG were present in such small concentrations that we were not able to evaluate the degree of conjugation reliably. In addition, colon polyphenols and theaflavins were primarily in their free forms.

In the second mouse experiment, we determined that concentrations of EC, EGCG, and ECG were decreased significantly after 1 d of feeding the control diet, whereas the initial ECG prostate concentration was very low and did not decrease significantly (**Fig. 3**).

Human study. A total of 20 participants completed the study. All patients had clinically localized prostate cancer. The demographic data and disease characteristics of the patients are shown in **Table 3**.

At the end of the daily consumption of 1.42 L of GT and BT (Table 2) for 5 d, prostate tissue samples had EGC, EC, EGCG, and ECG concentrations ranging from 21 to 107 pmol/g tissue (**Table 4**). Prostate PP concentrations showed a large variation between participants. The prostate concentrations of EGC, EGCG, and the sum of all 4 PPs were significantly greater in the tea intervention groups than in the SC group (Table 4). In a subgroup of prostate extracts, the identity of the polyphenols was confirmed using LC-ESI-MS (data not shown).

No polyphenols were detected by HPLC in the serum samples collected at baseline or after tea consumption (data not shown). The proliferation rate of LNCaP cells grown in media

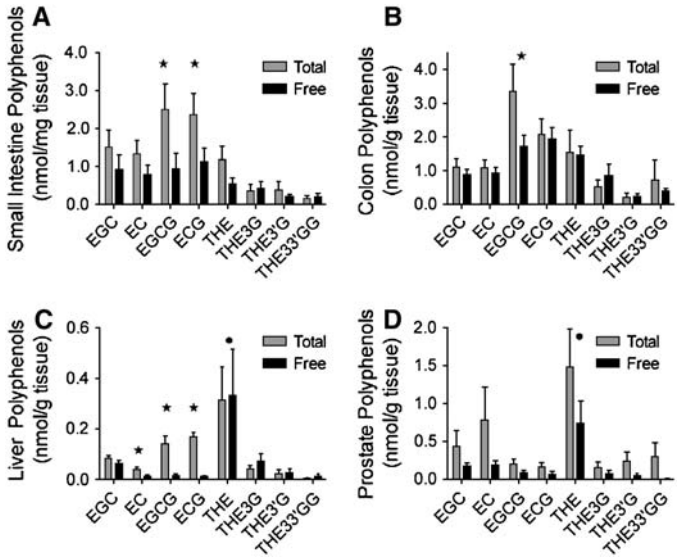

FIGURE 2 Total and free polyphenol and theaflavin concentration in C57BL/6 mouse liver, small intestine, colon, and prostate tissue. Values are means ± SD; $n = 4$–6. *Total is greater than free polyphenol and theaflavin concentrations. *Difference between EGCG and theaflavin concentrations. $P < 0.05$.

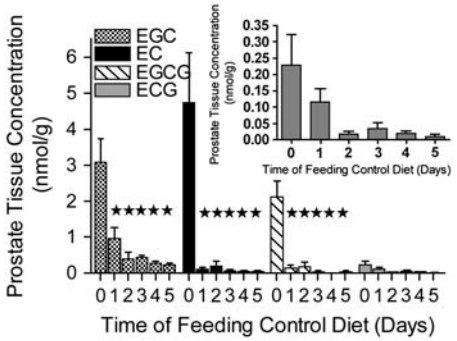

FIGURE 3 Concentration of polyphenols in prostate tissue of C57BL/6 mice fed a diet+GT extract for 2 wk before the control diet for 0–5 d. Values are means ± SD, $n = 4$. *Different from d 0, $P < 0.05$.

containing participants' serum collected after GT and BT consumption was significantly less than the proliferation of cells grown in media containing the serum obtained before tea consumption (**Fig. 4**). Serum obtained after BT consumption resulted in significantly less LNCaP proliferation relative to the serum afte soft drink consumption.

DISCUSSION

In the mouse study, the BT intervention provided 76.6 mg EGCG and 171.6 mg THE/kg body weight (BW). Prostate tissue concentrations were 0.24 nmol/g of EGCG and 1.5 nmol/g of THE. It appears that THE was absorbed and/or retained at a higher rate than EGCG. A mouse study by Lambert et al. (19) demonstrated that the intragastric administration of 50–2000 mg/kg BW of EGCG lead to a linear dose-relation in prostate (0.02–2.0 nmol/g), whereas in the small intestine and colon, EGCG tissue concentrations reached a plateau between 500 and 2000 mg/kg i.g. (19). A previous rat study found concentrations of 0.82, 0.81, and 0.126 nmol/g prostate tissue of EGC, EC, and EGCG, respectively (12), after rats were administered a 0.6% (wt:vol) (~177 mg of EGCG/kg BW) GT PP solution as the sole source of drinking fluid for 8 d. Compared with the animal studies, we found that in men, the prostate PP concentrations were 0.1, 0.04, and 0.07 nmol/g prostate for EGC, EC and EGCG after consumption of 1.42 L of brewed tea daily providing 3.5 and 4.1 mg of EGCG/kg BW for BT and GT, respectively. Higher doses of EGCG (20–500 × the human intake) were used in the animal studies compared with the human intake. As outlined below, it was demonstrated that the conjugation rate in mouse liver and intestine is higher compared with humans. Therefore, the relatively higher prostate tissue bioavailability of EGCG in humans compared with mice could be explained either by an increase in absorption or a decrease in conjugation, leading to a delay in excretion in humans compared with mice.

Once absorbed into the intestine, flavonoids undergo glucuronidation, sulfation, and/or methylation (20,21). Conjugated polyphenols were identified in human plasma (11,22,23), where EGCG was determined to be mainly in the free form (11,23). Our results of the BT intervention demonstrated that in mouse tissues, 55–90% of EGCG is conjugated, whereas THE is present mainly in the free form. Total PP concentrations determined in our study included the glucuronidated and sulfated, but not methylated form of PPs. Studies of EGCG- and EGC- glucuronidation revealed that mouse tissue had the highest catalytic efficiency followed by human and rat tissue (24). In our study, EGCG and EGC were conjugated more in livers of mice than in other tissues. Our knowledge about glucuronidation in the prostate is limited. One study by Sun et al. demonstrated that UDP-glucuronosyltransferase activity can be stimulated by several flavonoids in LNCaP prostate cancer cells, leading to a decrease in testosterone-stimulated prostate-specific antigen release(25). Sulfation was demonstrated to be catalyzed by sulfotransferases A1 and A3 in human and rat intestinal and human, mouse, and rat liver cytosol (22,26). A number of flavonoids were shown to modulate sulfotransferase activity in liver and intestinal tissue (27). Differences in the conjugation rate may also contribute to interindividual variations in the pharmacokinetics and biological activity of PPs in humans.

In human pharmacokinetic studies, it was demonstrated that the plasma concentration of PPs is maximal at 2–3 h after

TABLE 3

Demographics and disease characteristics of the men studied[1]

	BT	GT	SC
n	7	8	8
Age, *y*	62.3 ± 7.1	62.9 ± 7.9	62.4 ± 6.6
Height, *cm*	69.5 ± 2.5	70.8 ± 1.2	68.6 ± 4.4
Weight, *kg*	81.9 ± 12.6	85.8 ± 10.7	86.6 ± 7.0
Serum PSA, *μg/L*	4.3 ± 1.0	6.3 ± 2.9	4.9 ± 3.8
Gleason score[2]	6.3 ± 0.8	6.8 ± 1.0	6.2 ± 0.8

[1] Values are means ± SD.
[2] Mean score from the radical prostatectomy specimen.

TABLE 4

Concentration of tea polyphenols in human prostate tissue after GT, BT, or SC intervention[1,2]

	GT	BT	SC	*P*-value
	pmol/g prostate tissue			
n	8	7	5	
EGC	100 ± 22*	107 ± 22	0.1 ± 0	0.032
EC	43 ± 16	29 ± 13	7.3 ± 4	0.356
EGCG	40 ± 11	66 ± 10*	0 ± 0	0.01
ECG	21 ± 12	36 ± 26	2.3 ± 2	0.142
Sum	203 ± 32*	238 ± 33*	10 ± 6	0.0025

[1] Values are means ± SD. *Different from SC, $P < 0.05$.

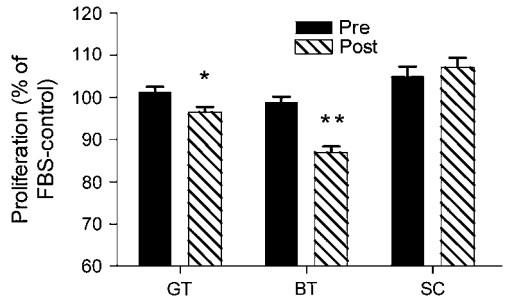

FIGURE 4 Effect of patient serum on LNCaP cell growth in vitro. Values are means ± SEM, $n = 6–7$. Asterisks indicate a difference from preintervention: *$P = 0.025$, **$P < 0.001$. Postcomparison of 3 interventions: post-BT vs. post-SC $P = 0.001$, post-GT vs. post-SC $P = 0.065$, and post-GT vs. post-BT $P = 0.065$.

administration and that all tea PPs are cleared from the plasma by 8 h (11). However, no earlier studies evaluated the turnover of tea polyphenols in tissue. Results of our mouse study demonstrate that EC, EGCG, and ECG decreased by 80–97% in the prostate after 24 h. The initital concentration of ECG was very small but decreased more slowly and was still detectable to 50% after 24 h and 15% on d 3 of consuming the control diet. Further studies are being performed to determine the tissue pharmacokinetics of theaflavins.

In the human study, due to the time elapsed from the last tea administration to the time of blood collection, no tea flavanols were found in serum. The participants drank the last cup of tea before midnight and blood was drawn between 7 and 8 h later while patients were prepared for surgery. However, LNCaP prostate cancer cell proliferation was significantly decreased when grown in medium containing patient serum collected after GT and BT consumption. Inhibition of cell proliferation by serum may have been the result of secondary metabolites of tea compounds or growth factors affected by tea polyphenols (e.g., the insulin-like growth factor-1:insulin-like growth factor binding protein3 ratio) (4). Possible candidates are polyphenol metabolites, including valerolactones or products from colonic microflora degradation such as 3,4-dihydroxyphenylacetic acid, 3-methoxyphenylacetic acid, and hippuric acid (28,29).

In conclusion, results from these studies demonstrated that BT and GT polyphenols and theaflavins are bioavailable in the prostate. The tissue bioavailability of polyphenols was greater in humans than in animals. In the mouse prostate, theaflavins were absorbed more than EGCG. Further studies of the conjugation pattern in human tissues are necessary to demonstrate whether results gained from studies in mice and rats are applicable to humans.

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