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Minireview

Role of epigallocatechin gallate (EGCG) in the treatment of breast and prostate cancer

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Abstract

Green tea and its major constituent epigallocatechin gallate (EGCG) have been extensively studied as a potential treatment for a variety of diseases, including cancer. Epidemiological data have suggested that EGCG may provide protective effects against hormone related cancers, namely breast or prostate cancer. Extensive in vitro investigations using both hormone responsive and non-responsive cell lines have shown that EGCG induces apoptosis and alters the expression of cell cycle regulatory proteins that are critical for cell survival and apoptosis. This review will highlight the important in vitro mechanistic actions elicited by EGCG in various breast and prostate cancer cell lines. Additionally, the actions of green tea/EGCG in in vivo models for these cancers as well as in clinical trials will be discussed.

Keywords: Epigallocatechin gallate; EGFR; Prostate cancer; Breast cancer; Apoptosis

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Introduction

Flavanoids are low-molecular weight plant-derived compounds found in fruits, vegetables, herbs, tea and wine (Middleton et al., 2000). They are divided into several different classes based on variations of the same basic structure. One such class is the flavan-3-ols, also referred to as the catechins, which are differentiated by di- or tri-hydroxyl group substitutions on the B ring and meta-5,7-dihydroxy substitution on the A ring (Yang et al., 2001). Catechins are especially concentrated in green tea (*Camellia sinensis*), accounting for 30–40% of its dry weight, while other flavonoids are present only in small quantities

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(Graham, 1992; Mukhtar et al., 1992; Arts et al., 2000a,b). The major catechins contained in green tea are (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECG), (−)-epicatechin (EC) and catechin (Fig. 1) (Graham, 1992; Mukhtar et al., 1992). EGCG, the most abundant catechin in green tea, is credited with the majority of health benefits associated with green tea consumption. EGCG has demonstrated beneficial effects in studies of Parkinson's disease (Choi et al., 2002), Alzheimer's disease (Choi et al., 2001; Obregon et al., 2006), stroke (Choi et al., 2004; Koh et al., 2006), obesity (Kao et al., 2000), diabetes (Anderson and Polansky, 2002; Tsuneki et al., 2004), chemoprevention (Xu et al., 1992; Katiyar et al., 1993; Kavanagh et al., 2001; Chung et al., 2003) and also possesses antioxidant activity (Guo et al., 1999). In this review, the potential applications of EGCG in the treatment of breast and prostate cancer and its possible mechanisms of action will be discussed.

Prostate cancer — in vitro effect of EGCG

Several studies have demonstrated a reduction in prostate cancer cell number in response to treatment with EGCG (Gupta et al., 2000; Bhatia and Agarwal, 2001; Chung et al., 2001; Hastak et al., 2003). For example, Gupta et al. (2000) demonstrated that EGCG dose-dependently reduced the cell number of both androgen dependent (expressing the androgen receptor (AR)), LNCaP, and independent (not expressing the AR), DU145, cells. This observation was verified by two studies which demonstrated similar effects on DU145 or LNCaP cell viability after treatment with EGCG (Chung et al., 2001; Hastak et al., 2003). It is important to utilize androgen responsive and unresponsive cell lines when testing potential anti-cancer agents as prostate tumors are composed of both androgen sensitive and insensitive cells (Agarwal, 2000; Adhami et al., 2003). Therefore, an effective treatment should induce death in both cell types. The mechanism through which EGCG induces death in prostate cancer cells has been identified as apoptosis (Gupta et al., 2000, 2003; Hastak et al., 2003). Furthermore, Gupta et al. (2000, 2003) demonstrated that the degree of apoptosis induction following EGCG treatment was similar in both DU145 and LNCaP cells. This suggests that the cytotoxic capacity of EGCG is not influenced by the presence or absence of the androgen receptor, which is a desirable attribute for a prostate cancer treatment.

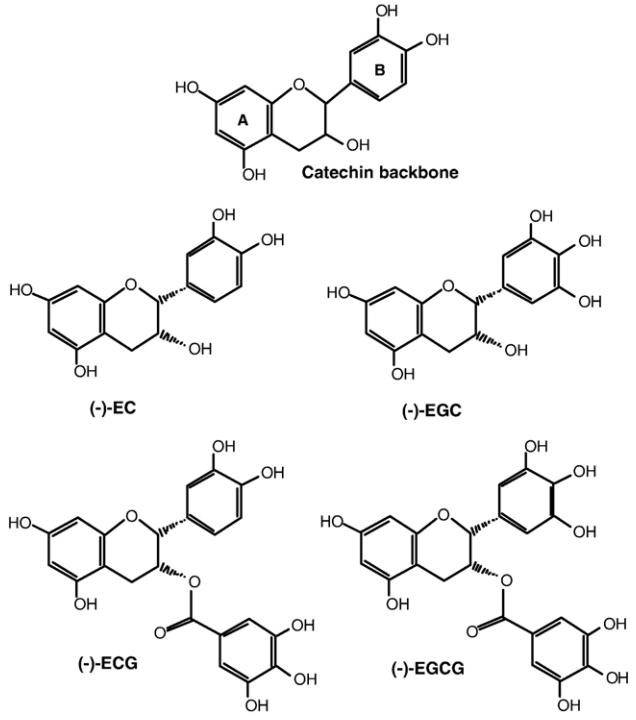

Fig. 1. The structure of the major catechins contained in green tea.

In vitro mechanisms of action

It has been reported that EGCG inhibits the activity of the epidermal growth factor receptor (EGFR) in prostate cancer cells (Bhatia and Agarwal, 2001). Activation of the EGFR, via auto-phosphorylation, leads to the activation of intracellular signaling cascades, such as the mitogen activated kinase pathway (MAPK) and phosphoinosital-3-kinase/AKT (PI3K/AKT) pathway (Casalini et al., 2004). Both of these pathways have roles in anti-apoptotic and growth stimulatory signaling (Pearson et al., 2001; Osaki et al., 2004). Several investigations have identified specific targets, modulated by EGCG, such as specific kinases of intracellular cell signaling cascades (Bhatia and Agarwal, 2001; Siddiqui et al., 2004). For example, EGCG treatment increased the proportion of phospho-ERK, an important signal transducing protein in the MAPK pathway (Bhatia and Agarwal, 2001; Siddiqui et al., 2004). Subsequent investigations demonstrated that EGCG treatment decreased the expression of phospho-PI3K and its substrate phospho-AKT to a similar extent in both DU145 and LNCaP cells. This information reaffirms that the effect of EGCG remains independent of the cell's AR status. Another important protein governing cell survival is the transfactor NF-κB. NF-κB has overlapping roles in many mitogenic signaling pathways as it is capable of promoting and repressing the expression of proteins involved in survival and apoptosis (Lin and Karin, 2003; Aggarwal, 2004; Monks et al., 2004). Therefore, it is vital for tumor growth, and accordingly, is an appropriate target in cancer treatment strategies. EGCG also modulates this transfactor, as it reduced NF-κB nuclear localization in prostate cancer cells regardless of their AR status (Hastak et al., 2003; Vayalil and Katiyar, 2004).

Cell cycle arrest can lead to the induction of apoptosis, however the mechanisms facilitating this remain largely unidentified (Hipfner and Cohen, 2004). EGCG has been shown to induce cell cycle arrest at the G_1 phase in both LNCaP and DU145 cells (Gupta et al., 2000, 2003; Bhatia and Agarwal, 2001). Progression through the G_1 phase is regulated through the cyclin dependent kinases (CDKs). The activity of the CDKs is in turn modulated by two sets of proteins; the cyclins (cyclin D1, D2 and E) and the cyclin dependent kinase inhibitors (CDKI: p21, p27, p16, p18). The cyclins are required by the CDKs to perform their catalytic activity, therefore these promote the progression through this cell cycle checkpoint.

Conversely, the CDKIs inhibit the kinase activity of the CDKs, thus inhibiting the progression from the G_1 phase through to the S phase (Orlowski and Furlanetto, 1996; Pavletich, 1999; Sherr and Roberts, 1999). Modulation of these proteins in prostate cancer cells by EGCG has been reported. Specifically, Gupta et al. (2000, 2003) demonstrated that EGCG increased the expression of p21, p27, p18 and p16 and decreased the expression of the cyclins D1, D2 and E as well as CDK 2, 4 and 6 in both LNCaP and DU145 cells. Moreover, the protein–protein interaction between the cyclins and CDKIs was increased. Thus, it appears that EGCG alters the expression of critical cell cycle regulatory proteins resulting in G_1 arrest. Again, this effect is independent of AR status.

Tumors require fresh nutrients, oxygen and a method of waste disposal for further growth and development. These requirements are fulfilled by the formation of new blood vessels which infiltrate the tumor: a process termed angiogenesis. In order for angiogenesis to occur, the connective tissue comprising the extracellular matrix around the tumor must be broken down to allow endothelial cells to migrate and form new blood vessels (Adhami et al., 2003; Gasparini et al., 2005; Harlozinska, 2005). Tumor cells achieve this through the release of matrix metalloproteinases (MMP), thus allowing for tumor metastasis. EGCG modulated this process at concentrations as low as 5 μg/ml, which inhibited the production of the zymogen and subsequent proteolytic activity of the MMPs in DU145 cells (Vayalil and Katiyar, 2004). Furthermore, EGCG inhibited the production of vascular endothelial growth factor (VEGF) in colon and breast cancer cells (Jung et al., 2001; Sartippour et al., 2002), and the activation of the VEGF receptor in leukemia and colon cancer cells (Jung et al., 2001; Lee et al., 2004). Therefore, EGCG inhibits various processes required for angiogenesis and metastasis in prostate cancer cells. This antiangiogenic effect coupled with the proapoptotic capacity of EGCG demonstrates that the growth of prostate cancer is inhibited via multiple mechanisms. This could be very important because overexpression of VEGF has occurred following resistance to EGFR inhibitors in ovarian and colon cancer murine xenograft models (Viloria-Petit et al., 2001; Ciardiello et al., 2004). Therefore, EGCG treatment may be able to overcome this problem by targeting both EGFR and VEGF.

Prostate cancer — effect of green tea in in vivo models

The transgenic adenocarcinoma of the mouse prostate (TRAMP) model is extensively used in chemopreventative studies, as it emulates the progressive form of prostate cancer. Green tea compounds have demonstrated chemopreventative activity in several studies using this model (Gupta et al., 2001; Adhami et al., 2004; Caporali et al., 2004). Gupta et al. (2001) illustrated a significant reduction in tumor incidence, burden and metastasis, prostate weight and cell proliferation in TRAMP mice following the administration of a 0.1% green tea polyphenol mixture (EGCG, ECG, EGC and EC) in the drinking water. This chemoprevention was accompanied by a reduction in serum insulin-like growth factor (IGF)-I levels and a corresponding increase in IGF-binding protein-3 (IGFBP-3) levels (Gupta et al., 2001). As an increase in IGF-I serum levels and a reduction in IGFBP-3 levels are associated with prostate cancer progression and a poor outcome in patients, modulation of IGF-I and IGFBP-3 may represent a mechanism for chemoprevention with green tea (Gupta et al., 2001). This was further investigated by Adhami et al. (2004). Specifically, TRAMP mice that received a 0.1% green tea polyphenol mixture exhibited lower levels of IGF-1 in the dorso-lateral prostate. Additionally, there were increased levels of IGFBP-3 and a reduction in phosphorylated PI3K, AKT and ERK1/2 compared to control mice. Green tea polyphenols also resulted in significantly reduced polypeptide levels of VEGF, urokinase plasminogen activator, MMP-2 and -9, and TIMP-1 and -2. The findings of Adhami et al. (2004) suggest that a green tea polyphenol mixture inhibits IGF-I signaling in TRAMP mice and this may contribute to the inhibition of prostate cancer progression and invasion.

A similar study conducted by Caporali et al. (2004) in TRAMP mice demonstrated a chemopreventative effect, as there was an 80% reduction in tumor development among mice that received a green tea polyphenol mixture (0.3% green tea polyphenol solution). Clusterin, a widely expressed tumor suppressor protein involved in apoptosis, was down-regulated in TRAMP mice that developed tumors, but was maintained in green tea polyphenol-treated mice. Recently, it has been documented that clusterin exerts regulatory control over NF-κB activity, which has been modulated by EGCG in vitro (Santilli et al., 2003). There is limited information regarding the activity of purified EGCG in prostate cancer models. One study by Liao et al. (1995) used purified EGCG in male athymic nude mice inoculated with 2 different human prostate cancer cell lines, PC-3 (androgen independent) or LNCaP 104-R (androgen dependent). The results showed that EGCG (1 mg/mouse/day, i.p., 14 days) significantly halted the growth of both androgen dependent and independent tumors, but was more effective at reducing the growth of androgen dependent tumors (Liao et al., 1995).

Prostate cancer risk associated with tea consumption

Epidemiological studies investigating the link between green tea consumption and prostate cancer risk are relatively few in number and have yielded conflicting results (Table 1). These studies either used few patients from a population at a low risk of prostate cancer (Jian et al., 2004; Chan et al., 2005) or did not discriminate between green and black tea consumption (Slattery and West, 1993; Jian et al., 1998). Therefore, no firm conclusions can be drawn between green tea consumption and the development of prostate cancer in humans.

Clinical trials with green tea extracts

Several clinical trials have been conducted to determine the ability of green tea extracts to prevent the development and progression of prostate cancer. (Bettuzzi et al. 2006) conducted a study using 60 volunteers with the predominant premalignant lesion of prostate cancer, termed high-grade prostate intraepithelial neoplasia. Patients received green tea compounds in capsule form (3, 200 mg capsules/day). Following one year of treatment, only 3% of patients that received the green tea

polyphenols presented with cancer compared with 30% in the placebo group. Furthermore, patients that received the green tea capsules exhibited a longer latency to tumor detection and exhibited an improved quality of life. Another clinical trial examined prostate-specific antigen (PSA) levels in 19 patients with hormone refractory prostate cancer following treatment with capsules containing green tea extract (250 mg, twice daily, 2 months) (Choan et al., 2005). No alterations in PSA levels were detected, and patients reported at least one side effect from the green tea capsules. The most common symptoms reported were abdominal discomfort and fatigue. Similarly, a Phase II clinical trial conducted by Jatoi et al. (2003) evaluated the ability of a green tea preparation (6 g green tea/day, 4 months) to sustain low levels of PSA in 42 patients with androgen-independent prostate carcinoma. Only one patient experienced a decline in PSA levels from 229 ng/dl to 105 ng/dl. However, this response was not maintained past two months and did not result in a reduction in tumor mass. Furthermore, 69% of patients reported Grade 1 or 2 toxicity, while six episodes of Grade 3 toxicity and one episode of Grade 4 toxicity also occurred. Although this suggests that green tea possesses limited antineoplastic activity, the trial was conducted in patients with androgen-independent prostate carcinoma, a subset of prostate cancers refractory to most treatment options. Additionally, most patients failed to complete the trial. Each of these clinical trails used green tea preparations containing caffeine, which has previously been reported to be responsible for gastrointestinal symptoms in a Phase I clinical trial (Pisters et al., 2001). Therefore, future trials should employ decaffeinated green tea extract preparations, or purified EGCG.

Breast cancer — in vitro effect of EGCG

EGCG is cytotoxic toward breast cancer cells regardless of their estrogen receptor (ER) status. For example, after treatment with EGCG, cell number was significantly decreased from control in the ER positive cell lines, MCF-7 and BT474 (Liang et al., 1999; Morre et al., 2000) as well as ER negative cell lines, Hs578t, MDA-MB-231, MBA-MB-468 and BT-20 (Liang et al., 1999; Morre et al., 2000; Kavanagh et al., 2001; Masuda et al., 2002, 2003; Chisholm et al., 2004; Roy et al., 2005). ER binding studies provided further evidence which demonstrated that the ER status of the cell lines is not important in EGCG-mediated cytotoxicity. Specifically, Goodin et al. (2002) demonstrated that EGCG weakly bound to both ERα and ERβ in vitro. However, EGCG failed to antagonize estradiol-mediated responses in female immature mice, while it weakly inhibited estradiol-mediated responses in ERβ reporter gene assays. These results suggest that EGCG is not a strong ER antagonist.

In vitro mechanisms of action

Very few studies have examined the mechanism by which EGCG is cytotoxic toward breast cancer cell lines. However, EGCG induces apoptosis in ER negative MDA-MB-468 (Roy et al., 2005) and MDA-MB-231 cells (Chisholm et al., 2004). A plethora of literature has detailed that EGCG induces apoptosis in many other human cancer cell lines (Ahmad et al., 1997; Chen et al., 1998, 2003; Masuda et al., 2001; Gupta et al., 2003). Therefore, it is likely that EGCG induces apoptosis in most, if not all, breast cancer cell lines. Mechanisms through which EGCG-induced apoptosis may be mediated include cell cycle arrest and changes in intracellular signaling cascades. Alterations in the CDKIs, p21 and p27, occur following EGCG treatment in breast cancer cells. For example, Liang et al. (1999) demonstrated that following treatment with EGCG, both p21 and p27 proteins were overexpressed in MCF-7 cells. This correlated well with cell cycle studies, which demonstrated that EGCG increased the proportion of cells arrested in G_1. Studies in the ER negative cell line, MDA-MB-231, showed a very similar trend, with increased protein expression of p21 and p27 following EGCG treatment (Masuda et al., 2002).

Table 1
Green tea consumption and prostate cancer risk

Population profile	Risk ratio (95% CI)		Outcome	Reference
White men in Utah, US	Tea consumption (cups/week):		No association	Slattery and West, 1993
–362 cases	≤67 years			
–685 controls	0	1.00		
	1–5	0.75 (0.47–1.20)		
	>5	1.06 (0.72–1.57)		
	>67 years			
	0	1.00		
	1–5	0.90 (0.47–1.75)		
	>5	0.90 (0.59–1.36)		
Three different regions in Canada	Tea consumption (g/day):		Tea intake is associated with a reduced risk of prostate cancer	Jian et al., 1998
–617 cases	0	1.0		
–637 controls	>0–500	0.89 (0.69–1.16)		
	>500	**0.70 (0.50–0.99)**		
Men in southeast China	Green tea consumption:		Green tea intake is associated with a reduced risk of prostate cancer	Jian et al., 2004
–130 cases	<1 cup/day	1.00		
–274 controls	1–3 cups/day	**0.53 (0.30–0.94)**		
	>3 cups/day	**0.27 (0.15–0.48)**		

Significant differences are indicated in bold typeface.

Table 2
Green tea consumption and breast cancer risk

Population profile	Risk ratio (95% CI)			Outcome	Reference
472 Japanese women with	Green tea consumption:			Green tea intake is associated	Nakachi et al., 1998
Stages I, II or III breast cancer	Stages I and II		**0.56 (0.35–0.91)**	with a reduced risk of recurrence	
	Stage III		1.88 (0.79–4.54)	of Stages I and II breast cancer	
34,759 women in Hiroshima	Green tea consumption:			No association	Key et al., 1999
and Nagasaki, Japan, including 427	≤1/day		1.0		
cases of primary breast cancer	2–4/day		1.02 (0.76–1.36)		
	≥5/day		0.86 (0.62–1.21)		
23,667 women, members	Green tea consumption:			No association	Nagano et al., 2001
of the Life Span Study Cohort,	≤1/day		1.0		
average age 56.8	2–4/day		1.2 (0.86–1.8)		
	≥5/day		1.0 (0.67–1.6)		
Japanese women, out-patients	Green tea consumption:			Green tea intake is associated	Inoue et al., 2001
at Aichi Cancer Center Hospital.	Stage I	≥3 cups/day	**0.43 (0.22–0.84)**	with a reduced risk of recurrence	
1160 patients with invasive		3–5 cups/day	**0.37 (0.17–0.80)**	in Stage I breast cancer	
breast cancer, average age 51.5		≥6 cups/day	0.59 (0.23–1.52)		
–751 cases Stage I	Stage II	≥3 cups/day	0.71 (0.35–1.44)		
–527 cases Stage II		3–5 cups/day	0.80 (0.38–1.69)		
–153 cases Stage III		≥6 cups/day	0.51 (0.18–1.46)		
	Stage III	≥3 cups/day	1.01 (0.50–2.05)		
		3–5 cups/day	1.06 (0.51–2.17)		
		≥6 cups/day	0.87 (0.33–2.27)		
Chinese, Japanese and Filipino	Green tea consumption:			Green tea intake is associated	Wu et al., 2003
women residing in the US,	0–85.7 ml/day		**0.74 (0.52–1.04)**	with a reduced risk of breast	
aged 25–74	≥85.7 ml/day		**0.61 (0.40–0.93)**	cancer	
Combined 2 cohort studies conducted in rural Japan	Green tea consumption:			No association	Suzuki et al., 2004
–17,353 women cohort 1	1–2 cups/day		0.87 (0.57–1.32)		
–24,769 women cohort 2	3–4 cups/day		1.07 (0.73–1.57)		
	≥5 cups/day		0.84 (0.57–1.24)		

Significant differences are indicated in bold typeface.

The induction of apoptosis and alterations in the cell cycle are likely to be the result of EGCG-mediated changes in intracellular pathways. It has been documented that EGCG alters the phosphorylative activity of the EGFR and its downstream targets in breast cancer cells. Specifically, Masuda et al. (2002) showed that treatment of MDA-MB-231 cells with EGCG inhibited both basal and TGF-α-induced EGFR auto-phosphorylation. It was further established that EGCG inhibited constitutive and TGF-α-induced AKT and STAT3 activity in these cells, but not the expression of phosphorylated ERK. Furthermore, Masuda et al. (2003) determined that EGCG inhibited the activity of the erbB2/HER-2 isoform of EGFR. This data correlates well with an EGCG-mediated decrease in c-fos promoter activity, a downstream effect of EGFR activation (Masuda et al., 2003). Furthermore, EGCG has been implicated in the modulation of NF-κB activity in breast cancer cell lines. Specifically, Masuda et al. (2002) demonstrated that EGCG inhibited the basal and inducible activity of the NF-κB complex in MDA-MB-231 cells. Finally, EGCG modulated the hepatocyte growth factor (HGF)/met signaling pathway involved in proliferation, survival and motility/invasion (Bigelow and Cardelli, 2006). Met is a tyrosine receptor kinase which autophosphorylates upon activation by its ligand, HGF. Downstream targets of this receptor include PI3K/AKT and MAPK pathways (Pearson et al., 2001; Casalini et al., 2004; Osaki et al., 2004; Bigelow and Cardelli, 2006). Bigelow and Cardelli (2006) determined that concentrations of EGCG as low as 0.6 μM inhibited HGF-induced Met phosphorylation, and subsequent AKT and ERK activation. Therefore, EGCG induces apoptosis in breast cancer cells by modulating intracellular signaling pathways that control cell cycle progression and this response is independent of the ER status of the cell line.

Breast cancer — effect of green tea in in vivo models

The majority of in vivo studies investigating the beneficial effects of green tea constituents in breast cancer chemoprevention have focused on green tea polyphenol mixtures rather than purified individual catechins. Studies of chemical-induced mammary carcinogenesis conducted in rats have demonstrated a protective effect of green tea compounds on tumor burden and survival, but it is still unclear whether this protection is greater at the pre- or post-initiation stage (Bhide et al., 1994; Hirose et al., 1994, 1997, 2002; Tanaka et al., 1997; Kavanagh et al., 2001). Various studies using either green tea extracts or purified EGCG have also been conducted using breast cancer cell xenografts in mice (Liao et al., 1995; Sartippour et al., 2001; Thangapazham et al., in press). Sartippour et al. (2001) used SCID mice inoculated with MDA-MB-231 breast cancer cells to illustrate that tumor growth, tumor weight and endothelial vessel density following green tea consumption decreased compared to control. Baliga et al. (2005) also demonstrated delayed tumor growth onset, rate of tumor growth, tumor volume and metastasis following a green tea polyphenol mixture in the drinking water of BALB/c mice inoculated with 4T1 mouse mammary carcinoma cells. These effects were associated with an increase in the Bax/

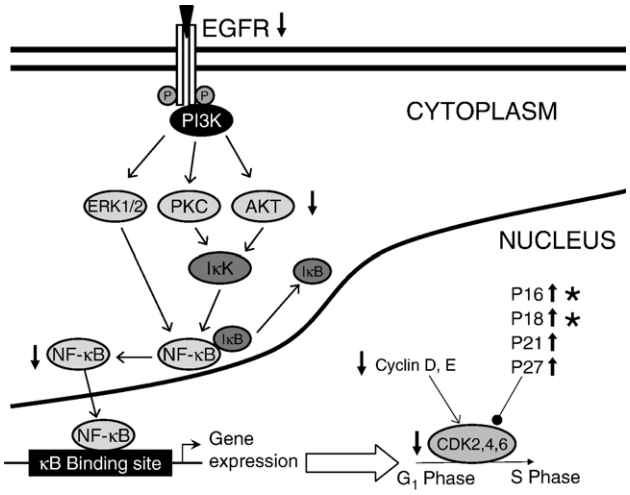

Fig. 2. Schematic diagram of intracellular cell survival signaling cascades that are activated following auto-phosphorylation of the EGFR, as well as proteins involved in the G_1-phase checkpoint. Arrows indicate an increase or decrease in the protein expression/activity following treatment with EGCG in both breast and prostate cancer cell lines. *Indicate that the effect has only been demonstrated in prostate cancer cells.

Bcl_2 ratio and caspase-3 activation. However, very few in vivo studies have examined the effects of purified EGCG. Specifically, Liao et al. (1995) demonstrated that EGCG (1 mg/animal/day, i.p., 14 days) reduced tumor size in female athymic nude mice inoculated with MCF-7 cells. More recently, Thangapazham et al. (in press) conducted a study using female athymic nude mice inoculated with MDA-MB-231 human breast cancer cells. Mice received 0.1% green tea polyphenols in the drinking water or EGCG (1 mg) by oral gavage. The treatments began on the day of cell inoculation and continued for 10 weeks. Both EGCG and the green tea polyphenol mixture suppressed tumor growth and burden, which suggests that EGCG is predominantly responsible for the chemopreventative activity of green tea.

Breast cancer risk associated with tea consumption and genotype

Epidemiological studies investigating the association between green tea consumption and breast cancer risk have yielded conflicting results (Table 2). Several studies have shown no association (Key et al., 1999; Nagano et al., 2001; Suzuki et al., 2004), while others have demonstrated a chemopreventative effect (Inoue et al., 2001; Wu et al., 2003). Given the inconsistency in the literature regarding chemoprevention with green tea, recent studies have genotyped breast cancer patients to determine whether the enzyme isoforms they possess could influence the protection conferred by green tea. A case–control study conducted among Chinese-, Japanese-, and Filipino-American women demonstrated that green tea intake was associated with a reduction in breast cancer risk, but only in women possessing a low-activity catechol-*O*-methyltransferase (COMT) allele (Wu et al., 2003). COMT is responsible for the rapid methylation of tea polyphenols and, therefore, differences in methylation capacity between individuals may alter the chemopreventative activity of green tea catechins. The findings of Wu et al. (2003) suggest that chemoprevention by green tea in women possessing the low-activity COMT allele may result from an increased bioavailability of catechins. Another recent study illustrated that green tea consumption is associated with a reduced risk of breast cancer in women possessing the high-activity, but not low-activity, angiotensin-converting enzyme (Yuan et al., 2005). This supports the hypothesis that a possible mechanism of chemoprevention by green tea catechins involves their inhibition of reactive oxygen species via angiotensin-converting enzyme inhibition.

A further mechanism of chemoprevention by green tea catechins involves the alteration of circulating hormone levels. A recent study by Wu et al. (2005) conducted in 130 post-menopausal women observed significantly lower plasma levels of estrone in women regularly consuming green tea compared with non- or irregular tea-drinkers (25.8 pg/ml vs 29.5 pg/ml). Plasma estradiol and androstenedione levels were also present in lower levels in women consuming green tea on a regular basis. The findings of Wu et al. (2005) suggest that alteration of estrone levels may contribute to the chemopreventative activity of green tea polyphenols.

Conclusions

EGCG induces apoptosis in both breast and prostate cancer cells in vitro. The cytotoxic effect of EGCG is not influenced by the hormone receptor status of either prostate or breast cancer cell lines. Furthermore, a ubiquitous mechanism may be responsible for the EGCG-mediated induction of apoptosis (Fig. 2). Upon treatment with EGCG, both breast and prostate cancer cells demonstrated cell cycle arrest in G_1 phase. This is likely to be the result of a decrease in the auto-phosphorylative capacity of EGFR and a subsequent reduction in the activity of intracellular signaling cascades, which are activated by EGFR. These changes may lead to alterations in the expression of proteins governing the cell cycle (Fig. 2). While these results are promising, this action has yet to be conclusively proven in in vivo models or in cancer patients.

References

Adhami, V.M., Ahmad, N., Mukhtar, H., 2003. Molecular targets for green tea in prostate cancer prevention. Journal of Nutrition 133, 2417s–2424s.

Adhami, V.M., Siddiqui, I.A., Ahmad, N., Gupta, S., Mukhtar, H., 2004. Oral consumption of green tea polyphenols inhibits insulin-like growth factor-I-induced signaling in an autochthonous mouse model of prostate cancer. Cancer Research 64, 8715–8722.

Agarwal, R., 2000. Cell signaling and regulators of cell cycle as molecular targets for prostate cancer prevention by dietary agents. Biochemical Pharmacology 60, 1051–1059.

Aggarwal, B.B., 2004. Nuclear Factor-kappaB: the enemy within. Cancer Cell 6, 203–208.

Ahmad, N., Feyes, D.K., Nieminen, A.-L., Agarwal, R., Mukhtar, H., 1997. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. Journal of the National Cancer Institute 89, 1881–1886.

Anderson, R.A., Polansky, M.M., 2002. Tea enhances insulin activity. Journal of Agriculture and Food Chemistry 50, 7182–7186.

Arts, I.C.W., van den Putte, C., Hollman, P.H.C., 2000a. Catechin contents of foods commonly consumed in the Netherlands: 1. Fruit, vegetables and processed foods. Journal of Agriculture and Food Chemistry 48, 1746–1751.

Arts, I.C.W., van den Putte, C., Hollman, P.H.C., 2000b. Catechin contents of foods commonly consumed in the Netherlands: 2. Tea, wine, fruit juices and chocolate milk. Journal of Agriculture and Food Chemistry 48, 1752–1757.

Baliga, M.S., Meleth, S., Katiyar, S.K., 2005. Growth inhibitory and antimetastatic effect of green tea polyphenols on metastasis-specific mouse mammary 4T1 cells in vitro and in vivo. Clinical Cancer Research 11, 1918–1927.

Bettuzzi, S., Brausi, M., Rizzi, F., Castagnetti, G., Peracchia, G., Corti, A., 2006. Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preclinical report from a one-year proof-of-principle study. Cancer Research 66, 1234–1240.

Bhatia, N., Agarwal, R., 2001. Detrimental effect of cancer preventative phytochemicals silymarin, genistein and epigallocatechin 3-gallate on epigenetic events in human prostate carcinoma DU145 cells. The Prostate 46, 98–107.

Bhide, S.V., Azuine, M.A., Lahiri, M., Telang, N.T., 1994. Chemoprevention of mammary tumor virus-induced and chemical carcinogen-induced mammary tumors by natural plant products. Breast Cancer Research and Treatment 30, 233–242.

Bigelow, R.L., Cardelli, J.A., 2006. The green tea catechins, (−)-epigallocatechin-3-gallate (EGCG) and (−)-epicatechin (ECG), inhibit HGF/Met signaling in immortalized and tumorigenic breast epithelial cells. Oncogene 25, 1922–1930.

Caporali, A., Davalli, P., Astancolle, S., D'Arca, D., Brausi, M., Bettuzzi, S., Corti, S., 2004. The chemopreventative action of catechins in the TRAMP mouse model of prostate carcinogenesis is accompanied by clusterin over-expression. Carcinogenesis 25, 2217–2224.

Casalini, P., Iorio, M.V., Galmozzi, E., Menard, S., 2004. Role of HER family in development and differentiation. Journal of Cellular Physiology 200, 343–350.

Chan, J.M., Gann, P.H., Giovannucci, E.L., 2005. Role of diet in prostate cancer development in progression. Journal of Clinical Oncology 23, 8152–8160.

Chen, Z.P., Schell, J.B., Ho, C.-T., Chen, K.Y., 1998. Green tea epigallocatechin gallate shows a pronounced growth inhibition of cancerous cells but not on their normal counterparts. Cancer Letters 129, 173–179.

Chen, C., Shen, G., Hebbar, V., Hu, R., Owuor, E.D., Kong, A.-N.T., 2003. Epigallocatechin-3-gallate-induced stress signals in HT-29 human colon adenocarcinoma cells. Carcinogenesis 24, 1369–1378.

Chisholm, K., Bray, B.J., Rosengren, R.J., 2004. Tamoxifen and epigallocatechin gallate are synergistically cytotoxic to MDA-MB-231 human breast cancer cells. Anticancer Drugs 15, 889–897.

Choan, E., Segal, R., Jonker, D., Malone, S., Reaume, N., Eapen, L., Gallant, V., 2005. A prospective trial of green tea for hormone refractory prostate cancer: an evaluation of the complementary/alternative therapy approach. Urologic Oncology 23, 108–113.

Choi, Y.T., Jung, C.H., Lee, S.R., Bae, J.H., Baek, W.K., Suh, M.H., Park, C.W., Suh, S.I., 2001. The green tea polyphenol (−)-epigallocatechin gallate attenuates beta-amyloid-induced neurotoxicity in cultured hippocampal neurons. Life Sciences 70, 603–614.

Choi, J.Y., Park, C.S., Kim, D.J., Cho, M.H., Jin, B.K., Pie, J.E., Chung, W.G., 2002. Prevention of nitric oxide-mediated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice by tea phenolic epigallocatechin 3-gallate. Neurotoxicity 23, 367–374.

Choi, Y.B., Kim, Y.I., Lee, K.S., Kim, B.S., Kim, D.J., 2004. Protective effect of epigallocatechin gallate on brain damage after transient middle cerebral artery occlusion in rats. Brain Research 1019, 47–54.

Chung, L.Y., Cheung, T.C., Kong, S.K., Fung, K.P., Choy, Y.M., Chan, Z.Y., Kwok, T.T., 2001. Induction of apoptosis by green tea catechins in human prostate cancer DU145 cells. Life Sciences 68, 1207–1214.

Chung, F.L., Schwartz, J., Herzog, C.R., Yang, Y.M., 2003. Tea and cancer prevention: studies in animals and humans. Journal of Nutrition 133, 3268S–3274S.

Ciardiello, F., Bianco, R., Caputo, R., Caputo, R., Damiano, V., Troiani, T., Melisi, S., De Vita, F., De Placido, S., Tortora, G., 2004. Antitumor activity of ZD6474, a vascular endothelial growth factor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to antiepidermal growth factor receptor therapy. Clinical Cancer Research 10, 784–793.

Gasparini, G., Longo, R., Toi, M., Ferrara, N., 2005. Angiogeneic inhibitors: a new therapeutic strategy in oncology. Nature Clinical Practice: Oncology 2, 562–577.

Goodin, M.G., Fertuck, K.C., Zacharewski, T.R., Rosengren, R.J., 2002. Estrogen receptor-mediated actions of polyphenolic catechins in vivo and in vitro. Toxicological Sciences 69, 354–361.

Graham, H., 1992. Green tea composition, consumption and polyphenol chemistry. Preventative Medicine 21, 334–350.

Guo, Q., Zhao, B., Shen, S., Hoou, J., Hu, J., Xin, W., 1999. ESR study on the structure–antioxidant activity relationship of tea catechins and their epimers. Biochemical and Biophysical Acta 1427, 13–23.

Gupta, S., Ahmad, N., Nieminen, A.-L., Mukhtar, H., 2000. Growth inhibition, cell-cycle dysregulation, and induction of apoptosis by green tea constituient (−)-epigallocatechin-3-gallate in androgen-sensitive and androgen-insensitive human prostate carcinoma cells. Toxicology and Applied Pharmacology 164, 82–90.

Gupta, S., Hastak, K., Ahmad, N., Lewin, J.S., Mukhtar, H., 2001. Inhibition of prostate cancer carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. Proceedings of the National Academy of Sciences of the United States of America 98, 10350–10355.

Gupta, S., Hussain, T., Mukhtar, H., 2003. Molecular pathway for (−)-epigallocatechin-3-gallate-induced cell cycle arrest and apoptosis of human prostate carcinoma cells. Archives of Biochemistry and Biophysics 410, 177–185.

Harlozinska, A., 2005. Progress in molecular mechanisms of tumor metastasis and angiogenesis. Anticancer Research 133, 2417s–2424s.

Hastak, K., Gupta, S., Ahmad, N., Agarwal, M.K., Agarwal, M.L., Mukhtar, H., 2003. Role of p53 and NF-kB in epigallocatechin-3-gallate-induced apoptosis of LNCaP cells. Oncogene 22, 4851–4859.

Hipfner, D.R., Cohen, S.M., 2004. Connecting proliferation and apoptosis in development and disease. Nature Reviews: Molecular Cell Biology 5, 805–815.

Hirose, M., Hoshiya, T., Akagi, K., Futakuchi, M., Ito, N., 1994. Inhibition of mammary gland carcinogenesis by green tea catechins and other naturally occurring antioxidants in female Sprague–Dawley rats pretreated with 7,12-dimethylbenz[alpha]anthracene. Cancer Letters 83, 149–156.

Hirose, M., Mizoguchi, Y., Yaono, M., Tanaka, H., Yamaguchi, T., Shirai, T., 1997. Effects of green tea catechins on the progression or late promotion stage of mammary gland carcinogenesis in female Sprague–Dawley rats pretreated with 7,12-dimethylbenz[*a*]anthrancene. Cancer Letters 112, 141–147.

Hirose, M., Nishikawa, A., Shibutani, M., Imai, T., Shirai, T., 2002. Chemoprevention of heterocyclic amine-induced mammary carcinogenesis in rats. Environmental and Molecular Mutagenesis 39, 271–278.

Inoue, M., Tajima, K., Mizutina, M., Iwata, H., Iwase, T., Miura, S., Hirose, K., Hamajima, N., Tominaga, S., 2001. Regular consumption of green tea and the risk of breast cancer recurrence: follow-up study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. Cancer Letters 167, 175–182.

Jatoi, A., Ellison, N., Burch, P.A., Sloan, J.A., Dakhil, S.R., Sovotny, P., Tan, W., Fitch, T.R., Rowland, K.M., Young, C.Y.F., Flynn, P.J., 2003. A Phase II clinical trial of green tea in the treatment of patients with androgen independent metastatic prostate carcinoma. Cancer 97, 1442–1446.

Jian, L., Xie, L.P., Lee, A.H., Binns, C.W., 2004. Protective effect of green tea against prostate cancer: a case–control study in southeast China. International Journal of Cancer 108, 130–135.

Jian, M.G., Hislop, G.T., Howe, G.R., Burch, J.D., Ghadirian, P., 1998. Alcohol and other beverage use and prostate cancer risk among Canadian men. International Journal of Cancer 78, 707–711.

Jung, Y.D., Kim, M.S., Shin, B.A., Chay, K.O., Ahn, B.W., Liu, W., Bucana, C.D., Gallick, G.E., Ellis, L.M., 2001. EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. British Journal of Cancer 84, 844–850.

Kao, Y.H., Hiipakka, R.A., Liao, S., 2000. Modulation of obesity by a green tea catechin. The American Journal of Clinical Nutrition 72, 1232–1234.

Katiyar, S.K., Agarwaal, R., Mukhtar, H., 1993. Protective effects of green tea polyphenols administered by oral intubation against chemical carcinogen-induced forestomach and pulmonary neoplasia in A/J mice. Cancer Letters 73, 167–172.

Kavanagh, K.T., Hafer, L.J., Kim, D.W., Mann, K.K., Sherr, D.H., Rogers, A.E., Sonenshein, G.E., 2001. Green tea extracts decrease carcinogen-induced

mammary tumour burden in rats and rate of breast cancer cell proliferation in culture. Journal of Cellular Biochemistry 82, 387–398.
Key, T.J., Sharp, G.B., Appleby, P.N., Beral, V., Goodman, M.T., Soda, M., Mabuchi, K., 1999. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. British Journal of Cancer 81, 1248–1256.
Koh, S.H., Lee, S.M., Kim, H.Y., Lee, K.Y., Lee, Y.J., Kim, H.T., Kim, J., Kim, M.H., Hwang, M.S., Song, C., Yang, K.W., Lee, K.W., Kim, S.H., Kim, O.H., 2006. The effect of epigallocatechin gallate on suppressing disease progression of ALS model mice. Neuroscience Letters 395, 103–107.
Lee, Y.K., Bone, N.D., Strege, A.K., Shanafelt, T.D., Jelinek, D.F., Kay, N.E., 2004. VEGF receptor phosphorylation status and apoptosis is modulated by a green tea component, epigallocatechin-3-gallate (EGCG), in B-cell chronic lymphocytic leukemia. Blood 104, 788–794.
Liang, Y.-C., Lin-Shiau, S.-Y., Chen, C.-F., Lin, J.-K., 1999. Inhibition of cyclin-dependent kinases 2 and 4 activities as well as induction of Cdk inhibitors p21 and p27 during growth arrest of human breast carcinoma cells by (−)-epigallocatechin-3-gallate. Journal of Cellular Biochemistry 75, 1–12.
Liao, S., Umekita, Y., Guo, J., Kokontis, J.M., Hiipakka, R.A., 1995. Growth inhibition and regression of human prostate and breast tumors in athymic mice by tea epigallocatechin gallate. Cancer Letters 96, 239–243.
Lin, A., Karin, M., 2003. NF-kappaB in cancer: a marked target. Seminars in Cancer Biology 13, 107–114.
Masuda, M., Suzui, M., Weinstein, I.B., 2001. Effects of epigallocatechin-3-gallate on growth, epidermal growth factor receptor signaling pathways, gene expression, and chemosensitivity in human head and neck squamous cell carcinoma cell lines. Clinical Cancer Research 7, 4220–4229.
Masuda, M., Suzui, M., Lim, J.T., Deguchi, A., Soh, J.W., Weinstein, I.B., 2002. Epigallocatechin-3-gallate decreases VEGF production in head and neck and breast carcinoma cells by inhibiting EGFR-related pathways of signal transduction. Journal of Experimental Therapeutics and Oncology 2, 350–359.
Masuda, M., Suzui, M., Lim, J.T.E., Weinstein, I.B., 2003. Epigallocatechin-3-gallate inhibits activation of HER-2/neu and downstream signaling pathways in human head and neck and breast carcinoma cells. Clinical Cancer Research 9, 3486–3491.
Middleton, E.J., Kandaswami, C., Theoharides, T.C., 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacological Reviews 52, 673–751.
Monks, N.R., Biswas, D.K., Pardee, A.B., 2004. Blocking anti-apoptosis as a strategy for cancer chemotherapy: NF-kappaB as a target. Journal of Cell Biochemistry 92, 646–650.
Morre, L.B., Bridge, A., Wu, L.-W., Morre, D.M., 2000. Preferential inhibition by (−)-epigallocatechin-3-gallate of the cell surface NADH oxidase and growth transformed cells ion culture. Biochemical Pharmacology 60, 937–946.
Mukhtar, H., Wang, Z.Y., Katiyar, S.K., Agarwaal, R., 1992. Tea components: antitumorgenic and anticarcinogenic effect. Preventative Medicine 21, 351–360.
Nagano, J., Kono, S., Preston, D.L., Mabuchi, K., 2001. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki, Japan. Cancer Causes and Control 12, 501–508.
Nakachi, K., Suemasu, K., Suga, K., Takeo, T., Imai, K., Higashi, Y., 1998. Influence of drinking green tea on breast cancer malignancy among Japanese patients. Japanese Journal of Cancer Research 89 (3), 254–261.
Obregon, D.F., Rezai-Zadeh, K., Bai, Y., Sun, N., Hou, H., Ehrhart, J., Zeng, J., Mori, T., Arendash, G., Shytle, D., Town, T., Tan, J., 2006. ADAM10 activation is required for green tea-EGCG-induced alpha-secretase cleavage of amyloid precursor protein. Journal of Biological Chemistry 281, 16419–16427.
Orlowski, C.C., Furlanetto, R.W., 1996. The mammalian cell cycle in normal and abnormal growth. Endocrinology and Metabolism Clinics of North America 25, 491–502.
Osaki, M., Oshimura, M., Ito, H., 2004. PI3K-Akt pathway: its functions and alterations in human cancer. Apoptosis 9, 667–676.
Pavletich, N.P., 1999. Mechanisms of cyclin-dependent kinase regulation: structures of Cdks, their cyclin activators and Cip and INK4 inhibitors. Journal of Molecular Biology 287, 821–828.
Pearson, G., Robinson, F., Gibson, T.B., Xu, B.-E., Karandikar, M., Berman, K., Cobb, M.H., 2001. Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions. Endocrine Reviews 22, 153–183.
Pisters, K.M., Newman, R.A., Coldman, B., Chin, D.M., Khuri, F.R., Hong, W.K., Glisson, B.S., Lee, J.S., 2001. Phase I trial of oral green tea extract in adult patients with solid tumors. Journal of Clinical Oncology 19, 1830–1838.
Roy, A.M., Baliga, M.S., Katiyar, S.K., 2005. Epigallocatechin-3-gallate induces apoptosis in estrogen receptor-negative human breast cancer cells via modulation in protein expression of p53 and Bax and caspase-3. Molecular Cancer Therapeutics 4, 81–90.
Santilli, G., Aronow, B.J., Sala, A., 2003. Essential requirement of apolipoprotein J (clusterin) signaling for IKB expression and regulation of NF-kB activity. Journal of Biological Chemistry 278, 38214–38219.
Sartippour, M.R., Heber, D., Ma, J., Lu, Q., Go, V.L., Nguyen, M., 2001. Green tea and its catechins inhibit breast cancer xenografts. Nutrition and Cancer 40, 149–156.
Sartippour, M.R., Shao, Z.-M., Heber, D., Beatty, P., Zhang, L., Liu, C., Ellis, L., Liu, W., Go, V.L., Brooks, M.N., 2002. Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells. Nutrition and Cancer 132, 2307–2311.
Sherr, C.J., Roberts, J.M., 1999. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes and Development 13, 1501–1512.
Siddiqui, I.A., Adhami, V.M., Afaq, F., Ahmad, N., Mukhtar, H., 2004. Modulation of phosphatidylinositol-3-kinase/protein kinase B- and mitogen-activated protein kinase-pathways by tea polyphenols in human prostate cancer cells. Journal of Cellular Biochemistry 91, 232–242.
Slattery, M.L., West, D.W., 1993. Smoking, alcohol, coffee, tea, caffeine and theobromine: risk of prostate cancer in Utah (United States). Cancer Causes and Control 4, 559–563.
Suzuki, Y., Tsubono, Y., Nakaya, N., Suzuki, Y., Koizumi, Y., Tsuji, I., 2004. Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. British Journal of Cancer 90, 1361–1363.
Tanaka, H., Hirose, M., Kawabe, M., Sano, M., Takesada, Y., Hagiwara, A., Shirai, T., 1997. Post-initiation inhibitory effects of green tea catechins on 7,12-dimethylbenz[a]anthracene-induced mammary gland carcinogenesis in female Sprague–Dawley rats. Cancer Letters 116, 47–52.
Thangapazham, R.L., Singh, A.K., Sharma, A., Warren, J., Gaddipati, J.P., Maheshwari, R.M., in press. Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo. Cancer Letters.
Tsuneki, H., Ishizuka, M., Terasawa, M., Wu, J.B., Sasaoka, T., Kimura, I., 2004. Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic (db/db) mice and on glucose metabolism in healthy humans. BMC Pharmacology 4, 18.
Vayalil, P.K., Katiyar, S.K., 2004. Treatment of epigallocatechin-3-gallate inhibits matrix metalloproteinases-2 and -9 via inhibition of activation of mitogen-activated protein kinases, c-jun and NF-kB in human prostate carcinoma DU-145 Cells. The Prostate 59, 33–42.
Viloria-Petit, A., Crombet, T., Jothy, S., Hicken, D., PBohlen, P., Schlappi, J.M., Rak, J., Kerbel, R.S., 2001. Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. Cancer Research 61, 5090–5101.
Wu, A.H., Yu, M.C., Tseng, C., Hankin, J., Pike, M.C., 2003. Green tea and risk of breast cancer in Asian Americans. International Journal of Cancer 106, 574–579.
Wu, A.H., Arakawa, K., Stanczyk, F.Z., Van Den Burg, D., Koh, W., Yu, M.C., 2005. Tea and circulating estrogen levels in postmenopausal Chinese women in Singapore. Carcinogenesis 26, 976–980.
Xu, Y., Ho, C.T., Amin, S.G., Han, C., Chung, F.L., 1992. Inhibition of tobacco-specific nitrosamine-induced lung tumorigenesis in A/J mice by green tea and its major polyphenol as antioxidants. Cancer Research 52, 167–172.
Yang, C.S., Prabhu, S., Landau, J., 2001. Prevention of carcinogenesis by tea polyphenols. Drug Metabolism Reviews 33, 237–253.
Yuan, J., Koh, W., Sun, C., Lee, H., Yu, M.C., 2005. Green tea intake, ACE gene polymorphism and breast cancer risk among Chinese women in Singapore. Carcinogenesis 26, 1389–1394.