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TOPIC HIGHLIGHT

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Green tea compounds in breast cancer prevention and treatment

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Abstract

Breast cancer is the most common cancer among women. In recent years, many *in vitro* and *in vivo* studies indicate that green tea possesses anti-cancer effects. The epidemiological studies, however, have produced inconclusive results in humans. Likewise, results from animal models about the preventive or therapeutic effects of green tea components are inconclusive. The mechanisms by which green tea intake may influence the risk of breast cancer in humans remain elusive mechanisms by which green tea intake may influence. Here, we review recent studies of green tea polyphenols and their applications in the prevention and treatment of breast cancer. Furthermore, we discuss the effect of green tea components on breast cancer by reviewing epidemiological studies, animal model studies and clinical trials. At last, we discuss the mechanisms by which green tea components suppress the development and recurrence of breast cancer. A better understanding of the mechanisms will improve the utilization of green tea in breast cancer prevention and therapy and pave the way to novel prevention and treatment strategies for breast cancer.

Key words: Breast cancer; Green tea; Epigallocatechin-3-gallate; Chemoprevention; Treatment

Core tip: Green tea components, especially epigallocatechin-3-gallate, possess anti-breast cancer effects. However, their effects on breast cancer prevention and therapy are still inconclusive. The anti-tumor mechanisms of green tea remain elusive. This review focuses on epidemiological and animal studies on green tea components against tumorigenesis, as well as possible mechanisms involved.

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INTRODUCTION

Breast cancer is a malignant proliferation of epithelial cell lining the ducts or lobules of the breast. Breast cancer is still the most common cancer among women[1]. According to the National Cancer Institute, 232340 new cases of female breast cancer and 2240 new cases of male breast cancer were reported in the United States in 2013, as well as about 39620 deaths caused by this disease. While there has been a steady decrease in breast cancer incidence and mortality since the early 90s[1], due largely to improvements in the early detection and treatment of breast

tumors[2], the social and economic impact of this malignancy continues to be enormous[3]. Many risk factors can impact on a woman's likelihood of developing breast cancer[4]. For those who are at a high risk for breast cancer, chemoprevention may be an alternative intervention to inhibit or delay carcinogenesis.

Green tea is the distinctive "liquor" produced from the evergreen plant Camellia sinensis leaves and is the most ancient beverage in the world. Traditional Chinese medicine has recommended drinking green tea for the prevention of disease. In recent years, many scientific and medical studies suggested that green tea possesses antiproliferative, antimutagenic, antioxidant, antibacterial, antiviral and chemopreventive effects[5]. Green tea contains large amounts of various flavonoids. A major class of flavanoids is catechins, which include epicatechin (EC), epigallocaetchin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG)[6]. EGCG is the most abundant catechin and accounts for 50%-75% of the total amount of catechins. Also, EGCG appears to be the most effective constituent of green tea[7]. Green tea polyphenols, and its major constituent EGCG, have been tested in tissue culture, animals and more recently in clinical trials[5]. In this review, we will highlight the recent studies on tea polyphenols and their applications in the prevention and treatment of breast cancer.

GREEN TEA AND BREAST CANCER PREVENTION: EPIDEMIOLOGICAL STUDIES

Over the past three decades, green tea has attracted increasing attention for its health benefits, especially anticancer effects[8]. As early as 1997[9],there was an epidemiological study showed that increased consumption of green tea had a potentially preventive effect on breast cancer in a Japanese population, especially among females drinking more than 10 cups a day. Since then, the association between green tea consumption and breast cancer risk has been extensively investigated. To date, three meta-analyses[10-13] have been published on the association between green tea and breast cancer risk and/or recurrence.

The most recent meta-analyses included two studies of breast cancer recurrence and seven studies of breast cancer incidence[11,14-20]. Among the two studies of breast cancer recurrence, both found a non-significant reduction in recurrence among heavy green tea drinkers (> 3 cups a day)[14,15]. There was no significant heterogeneity among the studies (P = 0.65, I^2 = 0%). This analysis suggested a marginally significant reduction of 27% in recurrence among heavy green tea drinkers (> 3 cups a day) (summary RR = 0.73, 95%CI: 0.56-0.96) when compared to non-drinkers. Among the breast cancer incidence studies, two were cohort studies and five were case-control studies[16-20]. Overall, there was a statistically significant reduction of 19% among women with high green tea intake (summary RR = 0.81, 95%CI: 0.75-0.88). Case-control studies suggested an identical effect as the overall analysis with a 19% reduction in risk among green tea drinkers (summary RR = 0.81, 95%CI: 0.75-0.88). However, when cohort studies were analyzed separately, no association between green tea consumption and breast cancer incidence was observed (summary RR = 0.85, 95%CI:0.65-1.22). In the second meta-analysis, seven studies were included for analyses[16-18,21,22]. The pooled RR of developing breast cancer for the highest levels of green tea consumption in cohort studies was 0.89 (95%CI: 0.71-1.1, P = 0.28, I^2 = 0%), and in case control studies, the odds ratio was 0.44 (95%CI: 0.14-1.31, P = 0.14, I^2 = 47%). In summary, these meta-analyses did not find a significant effect of green tea on breast cancer prevention. For the 2 studies that assessed risk of breast cancer recurrence in relation to green tea consumption, both were cohort studies (n = 1632)[15,23]. The pooled RR for breast cancer recurrence in all stages was 0.75 (95%CI: 0.47-1.19, P = 0.22, I^2 = 37%). A subgroup analysis of recurrence in stage I and II disease showed a pooled RR of 0.56 (95%CI: 0.38-0.83, P = 0.004, I^2 = 0%). These data indicate that high intake of green tea may be associated with a relative risk reduction in stage I and II breast cancer recurrence.

The epidemiological studies on the association between green tea and breast cancer remain inconclusive[24,25]. Remarkably, green tea may also interact with other bioactive dietary components, such as those in soy and mushroom, to affect breast cancer risk. A study in Asian-American women demonstrated a statistically significant inverse association between green tea and breast cancer risk among women with low soy intake, but not among women with high soy intake[26]. A case-control study indicated that higher dietary intake of mushrooms decreased breast cancer risk in pre- and postmenopausal Chinese women, and an additional decreased risk of breast cancer from joint effect of mushrooms and green tea was observed. These data suggested that combined green tea composition with other bioactive dietary components may be an appropriate way to improve its effects in cancer prevention. However, additional studies are required to elucidate the potential mechanisms of action.

GREEN TEA COMPONENTS AND BREAST CANCER: *IN VIVO* EXPERIMENTAL STUDIES

Green tea components and breast cancer prevention in animal models or clinical trials

"Cancer chemoprevention" was first introduced by M. Sporn, who defined it as the prevention of the occurrence of cancer by the oral administration of one or multiple compounds[27]. In 1987, the chemopreventive effect of EGCG was first reported when the inhibitory effects of EGCG on teleocidin-induced tumor promotion in mouse skin was observed[28]. There is an increasing

amount of evidence that has been presented, indicating that green tea may be chemopreventive[29]. Here, we focus on several recent studies about the effects of green tea components on breast carcinogenesis in animal models or clinical trials (Table 1).

Kavanagh *et al*[30]showed that a green tea extract significantly increases mammary tumor latency and decreases tumor weight and metastases in dimethyl-benzanthracene (DMBA) treated rats. Sakata and co-workers showed that green tea, alone or in combination with other anticancer components, may have significant chemopreventive effects on carcinogen-induced mammary tumorigenesis[31]. In the DMBA-induced mammary cancer rat models, the number of tumors per rat and the time latency to tumor development were estimated. However, animals exposed throughout life to EGCG in the drinking water showed no significant difference compared with the control group with respect to second and third tumor latency, although there was a decrease in the latency to first tumor development. Furthermore, the number of tumors per rat in EGCG-exposed rats was not significantly different from that in the controls. The authors suggested that the lack of effect of EGCG was because of the low bioavailability of pure EGCG. In 2012, Crew *et al*[32]reported results from a phase Ib clinical trial using EGCG over a 6-mo period, which was conducted to determine the maximum tolerated dose (MTD)[32,33]. During the treatment period no changes in breast tissue proliferation were observed. Overall, the agent was well-tolerated, with toxicity data establishing a 600 mg twice daily MTD for polyphenon E (Poly E). A phase Ⅱ trial testing the cancer preventive effects of 1 year of EGCG in postmenopausal women with high mammographic is currently ongoing, and the results are expected.

Green tea components and breast cancer therapy in animal models

So far, numerous studies have investigated the therapeutic effects of green tea on breast cancer using different rodent models and a variety of green tea products including green tea mixtures as well as specific catechins[38]. The recent studies of green tea catechins for breast cancer treatment in animal models are summarized in Table 2.

One recent study showed that treatment with EGCG at 50 to 100 mg/kg per day in drinking water significantly inhibited the progression of breast cancer in female mice. A further study suggested that the effect of EGCG on tumour size was mediated by the inhibition of hypoxia-inducible factor 1α (HIF-1α) and nuclear factor κB (NF-κB) activation as well as vascular endothelial growth factor (VEGF) expression[39].Another study demonstrated that EGCG significantly reduced tumor volume in a xenograft mouse model developed using stem-like SUM-149 breast cancer cells[40].

Remarkably, one study showed that high-dose green tea extracts strongly activated HIF-1 in T47D human breast carcinoma cells, and increased the expression of HIF-1 target genes including glucose transporter (GLUT)-1, VEGF, and p21/CDKN1A[41]. These results suggest that intended cancer chemoprevention with high-dose green tea extracts may be compromised by the ability of tea catechins to promote tumor cell survival pathways associated with HIF-1 activation. Therefore, the possibility of antagonistic interactions must be taken into account in the development of new cancer therapy strategies based on drug-EGCG co-treatments.

In breast cancer, EGCG has been shown to interfere with estrogen receptor function, inhibit estrogen-induced breast cancer cell proliferation, and sensitize hormone responsive tumors to drugs that target steroid receptors (*e.g.,*tamoxifen)[44-46]. The combination of EGCG and curcumin was efficacious in both *in vitro* and *in vivo* models of ERα- breast cancer. Also, our study showed that EGCG overcame paclitaxel-induced 78 kDa glucose-regulated protein (GRP78) expression and potentiated paclitaxel-induced Jun N-terminal kinase (JNK) phosphorylation in 4T1 cells both *in vitro* and *in vivo*[47]. When tumor-bearing mice were treated with paclitaxel in combination with EGCG, tumor growth was significantly inhibited, whereas the single-agent activity of paclitaxel or EGCG was poor. In addition, a clinical trial conducted recently in breast cancer patients undergoing radiotherapy showed that EGCG could potentiate the effect of ionizing radiation[48]. After two to eight weeks of EGCG plus radiotherapy administration, serum levels of angiogenic factors VEGF, hepatocyte growth factor, and active matrix metalloproteinase (MMP)-2 and MMP-9 were lower compared to those in patients receiving only radiotherapy. In addition, the antioxidant and anti-inflammatory activities of green tea catechins have been suggested to contribute to the potential protective role of EGCG against chemotherapy and radiotherapy side effects[49]. The use of green tea components, especially EGCG, could enhance the effect of conventional cancer therapies through additive or synergistic effects as well as through amelioration of deleterious side effects. Further research, especially at the clinical level, is needed to ascertain the potential role of EGCG as an adjuvant in breast cancer therapy.

MECHANISMS OF ACTION OF GREEN TEA COMPONENTS IN BREAST CANCER

To better understand the preventive and therapeutic activities of green tea components on breast cancer found in animal studies, substantial research has been conducted to uncover the mechanisms at cellular and molecular levels. Experimental studies collectively show that green tea components lead to wide range of responses in animal models or breast cancer cells.

Anti-angiogenesis

Induction of new blood vessel growth, known as angiogenesis, is required for tumor growth and metastasis[50]. Angiogenesis permits rapid tumor growth by providing an exchange of nutrients, oxygen, and paracrine stimuli to the tumor. A recent study showed that EGCG treat-

Table 1 Studies of green tea catechins on mammary tumorigenesis in animal models or clinical trials

Ref.	Model	Intervention	Main results
Kavanagh *et al*[30], 2001	4-wk-old female Sprague-Dawley rats	Treated with green tea catechins after exposure to DMBA	Green tea extract given after initiation significantly increases mammary tumor latency and decreases tumor weight and metastases in DMBA-treated rats
Hirose *et al*[34], 2002	6-wk-old female F344 rats	PhIP alone or PhIP plus 1% green tea catechins for 52 wk	1% green tea catechins were associated only with reduced mean size of mammary tumors without affecting the total number of mammary tumors
Whitsett *et al*[35] ,2006	Female Sprague–Dawley CD rats	Treated with DMBA to induce breast cancer after previous exposure to green tea catechins or control diet throughout life	Animals exposed throughout life to EGCG in the drinking water showed a decrease in the latency to first tumor development, although there was no significant difference as compared with the control group with respect to second and third tumor latency. Furthermore, the number of tumors per rat in EGCG-exposed rats was not significantly different from the controls
Kaur *et al*[36], 2007	C3(1)SV40T, t antigen transgenic multiple mammary adenocarcinoma mice	Mice received green tea catechins in drinking water at 0.01% (w/v) for 25 wk, with water as control	Green tea catechins delayed carcinogenesis as evidenced by a significant decrease in the volume and size of tumors in the mice exposed to green tea extract
Lubet *et al*[37], 2007	50-d-old female Sprague-Dawley rats	Intravenous injection of methyl-nitrosourea (75 mg/kg bw) *via* the jugular vein. 5 d after treatment with the carcinogen, Poly E was given by gavage at 1000 and 333 mg/kg bw/d.	There was no effect of Poly E on the latency period of the mammary tumors. The high and low doses of Poly E decreased the number of mammary tumors by 14% and reduced the weight of the tumors by 30% and 21%, respectively
Sakata *et al*[31], 2011	C3H/OuJ mice carrying preneoplastic lesions	Treated with EGCG and tamoxifen alone or in combination	The tumor incidences were decreased in the green tea extract, tamoxifen, and green tea extract and tamoxifen groups. Importantly, in the group treated with green tea extract and tamoxifen, no tumors developed
Crew *et al*[32],2012	Women with a history of histologically confirmed resected stage Ⅰ-Ⅲ, estrogen and progesterone receptor negative breast carcinoma.	Participants received either Poly E delivering 400, 600, or 800 mg of EGCG (2-4 capsules) twice daily with food or matching placebo for 6 mo	(1) The MTD for Poly E should be 600 mg twice daily; (2) There was about a 70% reduction in serum estradiol levels (P = 0.05) and a significant decrease in SHBG (P = 0.03) at 6 mo compared with baseline in the Poly E group. However, these changes did not differ significantly compared with the placebo group due to smaller numbers; and (3) No changes in breast tissue proliferation were observed.

DMBA: Dimethyl-benzanthracene; EGCG: Epigallocatechin-3-gallate.

ment reduced plasma VEGF levels over the control mice and the EGCG-treated tumor had lesser micro-vessels than the control tumor. The down-regulation of VEGF expression by EGCG was associated with the inhibition of HIF-1α and NF-κB activation[39]. Consistently, administration of polyphenon E, a standardized green tea extract, at concentrations of 20 ng/μL or greater significantly decreased the formation of vascular structures. *In vivo*, quantification of micro-vessel density also indicated that polyphenon E drastically reduced angiogenesis in a dose-dependent manner[51]. Another *in vitro* study showed that green tea extracts and EGCG decreased the RNA levels of VEGF in MDA-MB231 cells[52]. Taken together, inhibition of VEGF transcription appeared to be one of the molecular mechanisms involved in the antiangiogenic effects of green tea, which may contribute to its potential use for breast cancer treatment and/or prevention.

Interaction with target proteins

The eight phenolic groups of EGCG can serve as hydrogen bond donors to many biomolecules. EGCG has been recently shown to bind with high affinity to several target proteins, including phosphoinositide 3 kinase (PI3K)[53],67-kDa laminin receptor[54], Ras-GTPase activating protein (GAP) SH3 domain-binding protein 1 (G3BP1)[55], Bcl-xL and Bcl-2[56], vimentin[57], Fyn[58], GRP78[59], 70 kDa zeta-associated protein (Zap-70)[60], insulin like growth factor 1 receptor (IGF-1R)[61] and so on. All these proteins have been demonstrated to be important for the inhibitory activity of EGCG in breast cancer cell lines or animal models.

Inhibition of cell signaling pathways

VEGF is the most significant regulator in the development of the vascular system and is commonly overexpressed in breast cancer. Green tea catechins, especially EGCG, inhibit tumor growth, proliferation, migration, and angiogenesis of breast cancer[39,52]. Overexpression of Her-2/neu, the second member of epidermal growth factor receptor (EGFR) family, has been seen in about 30% of breast cancers and was associated with poor overall survival. EGCG treatment reduces basal phosphorylation and constitutive activation of the Her-2/neureceptor[62,63]. Other investigators have demonstrated that EGCG blocks Wnt signaling through the HBP1 transcriptional repressor that was previously shown to inhibit Wnt signaling[64]. In addition, Bigelow and Cardelli have investigated the effect of EGCG on inhibition of the hepatocyte growth factor signaling pathway. The results showed that EGCG (0.3 mmol/L) could completely

Table 2 Studies of green tea catechins on breast cancer treatment in animal models

Ref.	Model	Intervention	Effect on tumor size	Main mechanisms
Gu *et al*[39], 2013	8-wk-old female C57BL/6 mice were inoculated with 10^6 E0771 cells into the left fourth mammary gland fat pad	After cells were inoculated, mice received EGCG (around 50-100 mg/kg per day) in drinking water for 4 wk and 8 control mice received water only	(1) Tumor cross section area reduced 65% ($P < 0.01$); (2) tumour weight reduced 68% ($P < 0.01$); and (3) no difference in body weight, heart weight, kidney weight, or urinary protein	Inhibition of vascular endothelial growth factor (VEGF) expression and tumor angiogenesis *via* inhibiting hypoxia-inducible factor 1α and nuclear factor κB activation
Mineva *et al*[40], 2013	6-wk-old female nonobese diabetic/severe combined immunodeficiency mice were implanted with 5×10^3 SUM-149 cells in the fourth inguinal mammary fat pad	After 25 d, mice were intraperitoneally injected with 16.5 mg/kg EGCG or control PBS five times a week for the first five weeks and daily for the last week	(1) Tumor volume decreased 37.7% ± 4.4%; (2) tumor weight decreased 28.6% ± 6.5%; and (3) the lymphatic vessel density at the periphery of tumors decreased in EGCG-treated mice	EGCG decreased levels of VEGF-D RNA and VEGF-D protein
Jang *et al*[42], 2013	4T1 cells (10^5) were injected subcutaneously into either side of the posterior flank of BALB/c mice	On the 7th, 9th, 11th days after cell injection, mice were intraperitoneally injected with either EGCG (10 mg/kg) or PBS control	On day 30 after cell injection, a significant decrease of tumor volume and weight was observed in the EGCG-treated group *vs* the control group ($P < 0.0005$)	EGCG inhibited expression of CSF-1, CCL-2, IL-6 and transforming growth factor-β, and induced tumor necrosis factor-α expression
Thangapazham *et al*[43], 2007	5-wk-old female athymic nude mice (NCr-nu/nu) were implanted with 5×10^6 MDA-MB-231 cells in the mammary fat pad	After cell inoculation, one group of animals received 1% polyphenols from green tea (GTP) as a sole source of drinking water and the other group received a dose of 1 mg/animal of EGCG or water as control	At the end of 10 wk, the tumor volume was reduced by 45% and 61% in the EGCG and GTP treated groups, respectively ($P < 0.05$). All animals appeared healthy with no loss of body weight	EGCG and GTP fed animals showed increased apoptosis and decreased proliferation

DMBA: Dimethyl-benzanthracene; EGCG: Epigallocatechin-3-gallate; VEGF: Vascular endothelial growth factor.

blocked phosphorylation of Met (HGF Receptor) and its downstream extracellular signal-regulated kinases 1 and 2 (ERK1/2), and Akt/protein kinase B (PKB)[65].

Inhibition of enzyme activities

Numerous *in vivo* and *in vitro* studies have been published on the anti-tumour and anti-proliferative properties of green tea. EGCG has been reported to inhibit a number of enzymes. For example, Liang *et al*[66] showed that cyclin-dependent kinase (CDK) 2 and CDK4 were inhibited by 30 μmol/L EGCG in MCF-7 breast cancer lines, and this was associated with cell cycle arrest in G_0 and G_1. Also, EGCG increased the expression of the CDK inhibitor p21 in human breast carcinoma cells. Another study found that EGCG inhibited p38-regulated/activated protein kinase (PRAK; $IC_{50} = 1$ μmol/L) and dual-specificity tyrosine-phosphorylated and regulated kinase 1A (DYRK1A; $IC_{50} = 0.33$ μmol/L), but did not inhibit CDK2[67]. A recent study shows that EGCG is an ATP-competitive inhibitor of both PI3K and mammalian target of rapamycin with K_i values of 380 and 320 nmol/L, respectively[53].

Induction of cell cycle arrest and apoptosis

Dysregulated cellular proliferation and apoptosis are a hallmark of cancer. Green tea extracts and EGCG are capable of inhibiting cell growth and inducing apoptosis *via* a variety of mechanisms. Recent studies showed that EGCG suppressed proliferation and growth of triple negative breast cancer Hs578T cells[68], estrogen and progesterone receptor positive human breast cancer cells[69], MMTV-Her-2/neu mammary gland tumor NF639 cells[63] and others[70]. Also, EGCG induced apoptosis in estrogen receptor negative MDA-MB-468[71] and MDA-MB-231 cells[72]. Therefore, it is likely that EGCG induces cell cycle arrest and apoptosis in most, if not all, breast cancer cell lines. EGCG increases protein expression of p21 and p27[73]. Green tea inhibited expression of Ki-67 in both benign and malignant cells[74]. EGCG alters the activity of EGFR and its downstream targets[75]. In addition, research showed that catechin hydrate increased the expression of pro-apoptotic genes caspase-3, -8, and -9 and TP53[70,76]. In addition, EGCG can mediate the retinoblastoma (pRb)-E2F/DP pathway, an important regulator of cell cycle arrest and apoptosis[77].

Effects on microRNAs

MicroRNAs (miRNAs) are small (about 22 bases), single stranded, endogenous, noncoding RNAs that negatively regulate the translation and/or stability of mRNAs. It could be affected by EGCG to cause subtle changes in multiple molecular targets and pathways. In 2010, the first global miRNA expression profile showed that there were 16 down-regulated and 7 up-regulated miRNAs in MCF-7 breast cancer cells treated with Polyphenon-60 green tea extract[78]. Remarkably, among the miRNAs down-regulated by Polyphenon 60 treatment, MiR-27a was the most dramatic[78]. MiR-27a directly targets FOXO1, a putative tumor suppressor, and regulates endogenous protein expression in MCF-7 breast cancer

cells[79]. In addition, Jang *et al*[42] found that EGCG up-regulates MiR-16 in tumor cells, which down-regulates IκB kinase α and subsequently induces IκB accumulation in tumor associated macrophages, and inhibits M2 polarization. These studies suggest that the ability of green tea components to regulate miRNA expression may be one of potential mechanisms for green tea in breast cancer prevention and treatment.

Other potential mechanisms

In addition to mechanisms discussed above, there were other mechanisms involved in anticancer effects of green tea components including DNA methylation, metabolism, endoplasmic reticulum stress response and so on. Treatment of breast cancer cells with EGCG results in promoter demethylation of human telomerase reverse transcriptase, retinoic acid receptor β2 and target of methylation-induced silencing 1[80,81]. These studies demonstrated that EGCG has the potential to reverse epigenetic changes. A pilot study in overweight breast cancer survivors showed that intake of decaffeinated green tea for 6 mo was associated with a slight reduction in body weight and improved high-density lipoprotein and glucose homeostasis[82]. Also, EGCG treatment inhibited the expression of fatty acid synthase in MCF-7 and AU565 human breast cancer cell lines by blocking heregulin[83]. And our studies showed that EGCG potentiates quercetin-, taxol- and vinblastine-induced activation of pro-apoptosis arms of the endoplasmic reticulum stress response, such as JNK phosphorylation, caspase-7 and poly (ADP-ribose) polymerase (PARP) cleavage[47,84,85]. In addition to these mechanisms discussed in breast cancer, there are other multiple mechanisms presented in colon, lung, prostate, ovarian and other cancers. It can be expected that further in-depth research on each of these specific mechanisms will uncover more details of the action of green tea in breast cancer prevention and therapy.

REFERENCES

1 **Rebecca SM,** Jemal A. Cancer statistics. *JAMA* 2013; **310**: 982 [PMID: 24002295 DOI: 10.1001/jama.2013.5289]
2 **Independent UKPoBCS.** The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; **380**: 1778-1786 [PMID: 23117178 DOI: 10.1016/S0140-6736(12)61611-0]
3 **Smigal C**, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, Thun M. Trends in breast cancer by race and ethnicity: update 2006. *CA Cancer J Clin* 2006; **56**: 168-183 [PMID: 16737949]
4 **Tirona MT**, Sehgal R, Ballester O. Prevention of breast cancer (part I): epidemiology, risk factors, and risk assessment tools. *Cancer Invest* 2010; **28**: 743-750 [PMID: 20636109 DOI: 10.3109/07357907.2010.494321]
5 **Schramm L.** Going Green: The Role of the Green Tea Component EGCG in Chemoprevention. *J Carcinog Mutagen* 2013; **4**: 1000142 [PMID: 24077764 DOI: 10.4172/2157-2518.1000142]
6 **Kanwar J**, Taskeen M, Mohammad I, Huo C, Chan TH, Dou QP. Recent advances on tea polyphenols. *Front Biosci* (Elite Ed) 2012; **4**: 111-131 [PMID: 22201858]
7 **Du GJ**, Zhang Z, Wen XD, Yu C, Calway T, Yuan CS, Wang CZ. Epigallocatechin Gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea. *Nutrients* 2012; **4**: 1679-1691 [PMID: 23201840 DOI: 10.3390/nu4111679]
8 **Cabrera C**, Artacho R, Giménez R. Beneficial effects of green tea--a review. *J Am Coll Nutr* 2006; **25**: 79-99 [PMID: 16582024]
9 **Imai K**, Suga K, Nakachi K. Cancer-preventive effects of drinking green tea among a Japanese population. *Prev Med* 1997; **26**: 769-775 [PMID: 9388788 DOI: 10.1006/pmed.1997.0242]
10 **Seely D**, Mills EJ, Wu P, Verma S, Guyatt GH. The effects of green tea consumption on incidence of breast cancer and recurrence of breast cancer: a systematic review and meta-analysis. *Integr Cancer Ther* 2005; **4**: 144-155 [PMID: 15911927 DOI: 10.1177/1534735405276420]
11 **Ogunleye AA**, Xue F, Michels KB. Green tea consumption and breast cancer risk or recurrence: a meta-analysis. *Breast Cancer Res Treat* 2010; **119**: 477-484 [PMID: 19437116 DOI: 10.1007/s10549-009-0415-0]
12 **Sun CL**, Yuan JM, Koh WP, Yu MC. Green tea, black tea and breast cancer risk: a meta-analysis of epidemiological studies. *Carcinogenesis* 2006; **27**: 1310-1315 [PMID: 16311246 DOI: 10.1093/carcin/bgi276]
13 **Dai Q**, Shu XO, Li H, Yang G, Shrubsole MJ, Cai H, Ji B, Wen W, Franke A, Gao YT, Zheng W. Is green tea drinking associated with a later onset of breast cancer? *Ann Epidemiol* 2010; **20**: 74-81 [PMID: 20006278 DOI: 10.1016/j.annepidem.2009.09.005]
14 **Nakachi K**, Suemasu K, Suga K, Takeo T, Imai K, Higashi Y. Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Jpn J Cancer Res* 1998; **89**: 254-261 [PMID: 9600118]
15 **Inoue M**, Tajima K, Mizutani M, Iwata H, Iwase T, Miura S, Hirose K, Hamajima N, Tominaga S. 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 Lett* 2001; **167**: 175-182 [PMID: 11369139]
16 **Key TJ**, Sharp GB, Appleby PN, Beral V, Goodman MT, Soda M, Mabuchi K. Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. *Br J Cancer* 1999; **81**: 1248-1256 [PMID: 10584890 DOI: 10.1038/sj.bjc.6690837]
17 **Suzuki Y**, Tsubono Y, Nakaya N, Suzuki Y, Koizumi Y, Tsuji I. Green tea and the risk of breast cancer: pooled analysis of two prospective studies in Japan. *Br J Cancer* 2004; **90**: 1361-1363 [PMID: 15054454 DOI: 10.1038/sj.bjc.6601652]
18 **Tao M,** Liu D, Gao L, Jin F. Association between green tea drinking and breast cancer risk. *Tumor* 2002; **22**: 11-15
19 **Inoue M**, Robien K, Wang R, Van Den Berg DJ, Koh WP, Yu MC. Green tea intake, MTHFR/TYMS genotype and breast cancer risk: the Singapore Chinese Health Study. *Carcinogenesis* 2008; **29**: 1967-1972 [PMID: 18669903 DOI: 10.1093/carcin/bgn177]
20 **Shrubsole MJ**, Lu W, Chen Z, Shu XO, Zheng Y, Dai Q, Cai Q, Gu K, Ruan ZX, Gao YT, Zheng W. Drinking green tea modestly reduces breast cancer risk. *J Nutr* 2009; **139**: 310-316 [PMID: 19074205 DOI: 10.3945/jn.108.098699]
21 **Nagano J**, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). *Cancer Causes Control* 2001; **12**: 501-508 [PMID: 11519758]
22 **Wu AH**, Yu MC, Tseng CC, Hankin J, Pike MC. Green tea and risk of breast cancer in Asian Americans. *Int J Cancer* 2003; **106**: 574-579 [PMID: 12845655 DOI: 10.1002/ijc.11259]
23 **Nakachi K**, Matsuyama S, Miyake S, Suganuma M, Imai K. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. *Biofactors* 2000; **13**: 49-54 [PMID: 11237198]

24 **Chung FL**, Schwartz J, Herzog CR, Yang YM. Tea and cancer prevention: studies in animals and humans. *J Nutr* 2003; **133**: 3268S-3274S [PMID: 14519825]

25 **Zhang M**, Holman CD, Huang JP, Xie X. Green tea and the prevention of breast cancer: a case-control study in Southeast China. *Carcinogenesis* 2007; **28**: 1074-1078 [PMID: 17183063 DOI: 10.1093/carcin/bgl252]

26 **Boyd NF**, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD. Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol* 2005; **6**: 798-808 [PMID: 16198986 DOI: 10.1016/S1470-2045(05)70390-9]

27 **Sporn MB**, Dunlop NM, Newton DL, Smith JM. Prevention of chemical carcinogenesis by vitamin A and its synthetic analogs (retinoids). *Fed Proc* 1976; **35**: 1332-1338 [PMID: 770206]

28 **Yoshizawa HT,** Fujiki H, Yoshida T, Okuda T, et al Antitumor promoting activity of (−)-epigallocatechingallate, the main constituent of "Tannin" in green tea. *Phytother Res* 1987; **1**: 44-47

29 **Fujiki H**, Suganuma M, Imai K, Nakachi K. Green tea: cancer preventive beverage and/or drug. *Cancer Lett* 2002; **188**: 9-13 [PMID: 12406542]

30 **Kavanagh KT**, Hafer LJ, Kim DW, Mann KK, Sherr DH, Rogers AE, Sonenshein GE. Green tea extracts decrease carcinogen-induced mammary tumor burden in rats and rate of breast cancer cell proliferation in culture. *J Cell Biochem* 2001; **82**: 387-398 [PMID: 11500915]

31 **Sakata M**, Ikeda T, Imoto S, Jinno H, Kitagawa Y. Prevention of mammary carcinogenesis in C3H/OuJ mice by green tea and tamoxifen. *Asian Pac J Cancer Prev* 2011; **12**: 567-571 [PMID: 21545231]

32 **Crew KD**, Brown P, Greenlee H, Bevers TB, Arun B, Hudis C, McArthur HL, Chang J, Rimawi M, Vornik L, Cornelison TL, Wang A, Hibshoosh H, Ahmed A, Terry MB, Santella RM, Lippman SM, Hershman DL. Phase IB randomized, double-blinded, placebo-controlled, dose escalation study of polyphenon E in women with hormone receptor-negative breast cancer. *Cancer Prev Res* (Phila) 2012; **5**: 1144-1154 [PMID: 22827973 DOI: 10.1158/1940-6207.CAPR-12-0117]

33 **den Hollander P**, Savage MI, Brown PH. Targeted therapy for breast cancer prevention. *Front Oncol* 2013; **3**: 250 [PMID: 24069582 DOI: 10.3389/fonc.2013.00250]

34 **Hirose M**, Nishikawa A, Shibutani M, Imai T, Shirai T. Chemoprevention of heterocyclic amine-induced mammary carcinogenesis in rats. *Environ Mol Mutagen* 2002; **39**: 271-278 [PMID: 11921198]

35 **Whitsett T**, Carpenter M, Lamartiniere CA. Resveratrol, but not EGCG, in the diet suppresses DMBA-induced mammary cancer in rats. *J Carcinog* 2006; **5**: 15 [PMID: 16700914 DOI: 10.1186/1477-3163-5-15]

36 **Kaur S**, Greaves P, Cooke DN, Edwards R, Steward WP, Gescher AJ, Marczylo TH. Breast cancer prevention by green tea catechins and black tea theaflavins in the C3(1) SV40 T,t antigen transgenic mouse model is accompanied by increased apoptosis and a decrease in oxidative DNA adducts. *J Agric Food Chem* 2007; **55**: 3378-3385 [PMID: 17407311 DOI: 10.1021/jf0633342]

37 **Lubet RA**, Yang CS, Lee MJ, Hara Y, Kapetanovic IM, Crowell JA, Steele VE, Juliana MM, Grubbs CJ. Preventive effects of polyphenon E on urinary bladder and mammary cancers in rats and correlations with serum and urine levels of tea polyphenols. *Mol Cancer Ther* 2007; **6**: 2022-2028 [PMID: 17620432 DOI: 10.1158/1535-7163.MCT-07-0058]

38 **Crespy V**, Williamson G. A review of the health effects of green tea catechins in in vivo animal models. *J Nutr* 2004; **134**: 3431S-3440S [PMID: 15570050]

39 **Gu JW**, Makey KL, Tucker KB, Chinchar E, Mao X, Pei I, Thomas EY, Miele L. EGCG, a major green tea catechin suppresses breast tumor angiogenesis and growth via inhibiting the activation of HIF-1α and NFκB, and VEGF expression. *Vasc Cell* 2013; **5**: 9 [PMID: 23638734 DOI: 10.1186/2045-824X-5-9]

40 **Mineva ND**, Paulson KE, Naber SP, Yee AS, Sonenshein GE. Epigallocatechin-3-gallate inhibits stem-like inflammatory breast cancer cells. *PLoS One* 2013; **8**: e73464 [PMID: 24039951 DOI: 10.1371/journal.pone.0073464]

41 **Zhou YD**, Kim YP, Li XC, Baerson SR, Agarwal AK, Hodges TW, Ferreira D, Nagle DG. Hypoxia-inducible factor-1 activation by (-)-epicatechin gallate: potential adverse effects of cancer chemoprevention with high-dose green tea extracts. *J Nat Prod* 2004; **67**: 2063-2069 [PMID: 15620252 DOI: 10.1021/np040140c]

42 **Jang JY**, Lee JK, Jeon YK, Kim CW. Exosome derived from epigallocatechin gallate treated breast cancer cells suppresses tumor growth by inhibiting tumor-associated macrophage infiltration and M2 polarization. *BMC Cancer* 2013; **13**: 421 [PMID: 24044575 DOI: 10.1186/1471-2407-13-421]

43 **Thangapazham RL**, Singh AK, Sharma A, Warren J, Gaddipati JP, Maheshwari RK. Green tea polyphenols and its constituent epigallocatechin gallate inhibits proliferation of human breast cancer cells in vitro and in vivo. *Cancer Lett* 2007; **245**: 232-241 [PMID: 16519995 DOI: 10.1016/j.canlet.2006.01.027]

44 **Farabegoli F**, Barbi C, Lambertini E, Piva R. (-)-Epigallocatechin-3-gallate downregulates estrogen receptor alpha function in MCF-7 breast carcinoma cells. *Cancer Detect Prev* 2007; **31**: 499-504 [PMID: 18061364 DOI: 10.1016/j.cdp.2007.10.018]

45 **Tu SH**, Ku CY, Ho CT, Chen CS, Huang CS, Lee CH, Chen LC, Pan MH, Chang HW, Chang CH, Chang YJ, Wei PL, Wu CH, Ho YS. Tea polyphenol (-)-epigallocatechin-3-gallate inhibits nicotine- and estrogen-induced α9-nicotinic acetylcholine receptor upregulation in human breast cancer cells. *Mol Nutr Food Res* 2011; **55**: 455-466 [PMID: 21370452 DOI: 10.1002/mnfr.201000254]

46 **Sartippour MR**, Pietras R, Marquez-Garban DC, Chen HW, Heber D, Henning SM, Sartippour G, Zhang L, Lu M, Weinberg O, Rao JY, Brooks MN. The combination of green tea and tamoxifen is effective against breast cancer. *Carcinogenesis* 2006; **27**: 2424-2433 [PMID: 16785249 DOI: 10.1093/carcin/bgl066]

47 **Luo T**, Wang J, Yin Y, Hua H, Jing J, Sun X, Li M, Zhang Y, Jiang Y. (-)-Epigallocatechin gallate sensitizes breast cancer cells to paclitaxel in a murine model of breast carcinoma. *Breast Cancer Res* 2010; **12**: R8 [PMID: 20078855 DOI: 10.1186/bcr2473]

48 **Zhang G**, Wang Y, Zhang Y, Wan X, Li J, Liu K, Wang F, Liu K, Liu Q, Yang C, Yu P, Huang Y, Wang S, Jiang P, Qu Z, Luan J, Duan H, Zhang L, Hou A, Jin S, Hsieh TC, Wu E. Anti-cancer activities of tea epigallocatechin-3-gallate in breast cancer patients under radiotherapy. *Curr Mol Med* 2012; **12**: 163-176 [PMID: 22280355]

49 **Alcaraz M**, Armero D, Martínez-Beneyto Y, Castillo J, Benavente-García O, Fernandez H, Alcaraz-Saura M, Canteras M. Chemical genoprotection: reducing biological damage to as low as reasonably achievable levels. *Dentomaxillofac Radiol* 2011; **40**: 310-314 [PMID: 21697157 DOI: 10.1259/dmfr/95408354]

50 **Folkman J**. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995; **1**: 27-31 [PMID: 7584949]

51 **Leong H**, Mathur PS, Greene GL. Green tea catechins inhibit angiogenesis through suppression of STAT3 activation. *Breast Cancer Res Treat* 2009; **117**: 505-515 [PMID: 18821062 DOI: 10.1007/s10549-008-0196-x]

52 **Sartippour MR**, Shao ZM, Heber D, Beatty P, Zhang L, Liu C, Ellis L, Liu W, Go VL, Brooks MN. Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells. *J Nutr* 2002; **132**: 2307-2311 [PMID: 12163680]

53 **Van Aller GS**, Carson JD, Tang W, Peng H, Zhao L, Copeland RA, Tummino PJ, Luo L. Epigallocatechin gallate (EGCG), a major component of green tea, is a dual phosphoinositide-3-kinase/mTOR inhibitor. *Biochem Biophys Res Commun* 2011; **406**: 194-199 [PMID: 21300025 DOI: 10.1016/j.bbrc.2011.02.010]

54 **Umeda D**, Yano S, Yamada K, Tachibana H. Green tea polyphenol epigallocatechin-3-gallate signaling pathway through 67-kDa laminin receptor. *J Biol Chem* 2008; **283**: 3050-3058 [PMID: 18079119 DOI: 10.1074/jbc.M707892200]

55 **Shim JH**, Su ZY, Chae JI, Kim DJ, Zhu F, Ma WY, Bode AM, Yang CS, Dong Z. Epigallocatechin gallate suppresses lung cancer cell growth through Ras-GTPase-activating protein SH3 domain-binding protein 1. *Cancer Prev Res* (Phila) 2010; **3**: 670-679 [PMID: 20424128 DOI: 10.1158/1940-6207.CAPR-09-0185]

56 **Leone M**, Zhai D, Sareth S, Kitada S, Reed JC, Pellecchia M. Cancer prevention by tea polyphenols is linked to their direct inhibition of antiapoptotic Bcl-2-family proteins. *Cancer Res* 2003; **63**: 8118-8121 [PMID: 14678963]

57 **Ermakova S**, Choi BY, Choi HS, Kang BS, Bode AM, Dong Z. The intermediate filament protein vimentin is a new target for epigallocatechin gallate. *J Biol Chem* 2005; **280**: 16882-16890 [PMID: 15713670 DOI: 10.1074/jbc.M414185200]

58 **He Z**, Tang F, Ermakova S, Li M, Zhao Q, Cho YY, Ma WY, Choi HS, Bode AM, Yang CS, Dong Z. Fyn is a novel target of (-)-epigallocatechin gallate in the inhibition of JB6 Cl41 cell transformation. *Mol Carcinog* 2008; **47**: 172-183 [PMID: 18095272 DOI: 10.1002/mc.20299]

59 **Ermakova SP**, Kang BS, Choi BY, Choi HS, Schuster TF, Ma WY, Bode AM, Dong Z. (-)-Epigallocatechin gallate overcomes resistance to etoposide-induced cell death by targeting the molecular chaperone glucose-regulated protein 78. *Cancer Res* 2006; **66**: 9260-9269 [PMID: 16982771 DOI: 10.1158/0008-5472.CAN-06-1586]

60 **Shim JH**, Choi HS, Pugliese A, Lee SY, Chae JI, Choi BY, Bode AM, Dong Z. (-)-Epigallocatechin gallate regulates CD3-mediated T cell receptor signaling in leukemia through the inhibition of ZAP-70 kinase. *J Biol Chem* 2008; **283**: 28370-28379 [PMID: 18687687 DOI: 10.1074/jbc.M802200200]

61 **Li M**, He Z, Ermakova S, Zheng D, Tang F, Cho YY, Zhu F, Ma WY, Sham Y, Rogozin EA, Bode AM, Cao Y, Dong Z. Direct inhibition of insulin-like growth factor-I receptor kinase activity by (-)-epigallocatechin-3-gallate regulates cell transformation. *Cancer Epidemiol Biomarkers Prev* 2007; **16**: 598-605 [PMID: 17372258 DOI: 10.1158/1055-9965.EPI-06-0892]

62 **Masuda M**, Suzui M, Lim JT, Weinstein IB. Epigallocatechin-3-gallate inhibits activation of HER-2/neu and downstream signaling pathways in human head and neck and breast carcinoma cells. *Clin Cancer Res* 2003; **9**: 3486-3491 [PMID: 12960141]

63 **Pianetti S**, Guo S, Kavanagh KT, Sonenshein GE. Green tea polyphenol epigallocatechin-3 gallate inhibits Her-2/neu signaling, proliferation, and transformed phenotype of breast cancer cells. *Cancer Res* 2002; **62**: 652-655 [PMID: 11830514]

64 **Kim J**, Zhang X, Rieger-Christ KM, Summerhayes IC, Wazer DE, Paulson KE, Yee AS. Suppression of Wnt signaling by the green tea compound (-)-epigallocatechin 3-gallate (EGCG) in invasive breast cancer cells. Requirement of the transcriptional repressor HBP1. *J Biol Chem* 2006; **281**: 10865-10875 [PMID: 16495219 DOI: 10.1074/jbc.M513378200]

65 **Bigelow RL**, Cardelli JA. The green tea catechins, (-)-Epigallocatechin-3-gallate (EGCG) and (-)-Epicatechin-3-gallate (ECG), inhibit HGF/Met signaling in immortalized and tumorigenic breast epithelial cells. *Oncogene* 2006; **25**: 1922-1930 [PMID: 16449979 DOI: 10.1038/sj.onc.1209227]

66 **Liang YC**, Lin-Shiau SY, Chen CF, Lin JK. 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. *J Cell Biochem* 1999; **75**: 1-12 [PMID: 10462699]

67 **Bain J**, McLauchlan H, Elliott M, Cohen P. The specificities of protein kinase inhibitors: an update. *Biochem J* 2003; **371**: 199-204 [PMID: 12534346 DOI: 10.1042/BJ20021535]

68 **Braicu C**, Gherman CD, Irimie A, Berindan-Neagoe I. Epigallocatechin-3-Gallate (EGCG) inhibits cell proliferation and migratory behaviour of triple negative breast cancer cells. *J Nanosci Nanotechnol* 2013; **13**: 632-637 [PMID: 23646788]

69 **De Amicis F**, Russo A, Avena P, Santoro M, Vivacqua A, Bonofiglio D, Mauro L, Aquila S, Tramontano D, Fuqua SA, Andò S. In vitro mechanism for downregulation of ER-α expression by epigallocatechin gallate in ER+/PR+ human breast cancer cells. *Mol Nutr Food Res* 2013; **57**: 840-853 [PMID: 23322423 DOI: 10.1002/mnfr.201200560]

70 **Alshatwi AA**. Catechin hydrate suppresses MCF-7 proliferation through TP53/Caspase-mediated apoptosis. *J Exp Clin Cancer Res* 2010; **29**: 167 [PMID: 21167021 DOI: 10.1186/1756-9966-29-167]

71 **Roy AM**, Baliga MS, Katiyar SK. Epigallocatechin-3-gallate induces apoptosis in estrogen receptor-negative human breast carcinoma cells via modulation in protein expression of p53 and Bax and caspase-3 activation. *Mol Cancer Ther* 2005; **4**: 81-90 [PMID: 15657356]

72 **Chisholm K**, Bray BJ, Rosengren RJ. Tamoxifen and epigallocatechin gallate are synergistically cytotoxic to MDA-MB-231 human breast cancer cells. *Anticancer Drugs* 2004; **15**: 889-897 [PMID: 15457130]

73 **Masuda M**, Suzui M, Lim JT, Deguchi A, Soh JW, Weinstein IB. Epigallocatechin-3-gallate decreases VEGF production in head and neck and breast carcinoma cells by inhibiting EGFR-related pathways of signal transduction. *J Exp Ther Oncol* 2002; **2**: 350-359 [PMID: 12440226]

74 **Yu Steven SSDV**, Hawes D, Tseng CC, Yang CS, Pike M C, Wu AH. Biological Effects of Green Tea Capsule Supplementation in Pre-surgery Postmenopausal Breast Cancer Patients. *Front Oncol* 2013; **3**: 298

75 **Farabegoli F**, Papi A, Orlandi M. (-)-Epigallocatechin-3-gallate down-regulates EGFR, MMP-2, MMP-9 and EMMPRIN and inhibits the invasion of MCF-7 tamoxifen-resistant cells. *Biosci Rep* 2011; **31**: 99-108 [PMID: 20446926 DOI: 10.1042/BSR20090143]

76 **Islam S**, Islam N, Kermode T, Johnstone B, Mukhtar H, Moskowitz RW, Goldberg VM, Malemud CJ, Haqqi TM. Involvement of caspase-3 in epigallocatechin-3-gallate-mediated apoptosis of human chondrosarcoma cells. *Biochem Biophys Res Commun* 2000; **270**: 793-797 [PMID: 10772904 DOI: 10.1006/bbrc.2000.2536]

77 **Ahmad N**, Adhami VM, Gupta S, Cheng P, Mukhtar H. Role of the retinoblastoma (pRb)-E2F/DP pathway in cancer chemopreventive effects of green tea polyphenol epigallocatechin-3-gallate. *Arch Biochem Biophys* 2002; **398**: 125-131 [PMID: 11811957 DOI: 10.1006/abbi.2001.2704]

78 **Fix LN**, Shah M, Efferth T, Farwell MA, Zhang B. MicroRNA expression profile of MCF-7 human breast cancer cells and the effect of green tea polyphenon-60. *Cancer Genomics Proteomics* 2010; **7**: 261-277 [PMID: 20952761]

79 **Guttilla IK**, White BA. Coordinate regulation of FOXO1 by miR-27a, miR-96, and miR-182 in breast cancer cells. *J Biol Chem* 2009; **284**: 23204-23216 [PMID: 19574223 DOI: 10.1074/jbc.M109.031427]

80 **Berletch JB**, Liu C, Love WK, Andrews LG, Katiyar SK, Tollefsbol TO. Epigenetic and genetic mechanisms contribute to telomerase inhibition by EGCG. *J Cell Biochem* 2008; **103**: 509-519 [PMID: 17570133 DOI: 10.1002/jcb.21417]

81 **Mirza S**, Sharma G, Parshad R, Gupta SD, Pandya P, Ralhan R. Expression of DNA methyltransferases in breast cancer pa-

tients and to analyze the effect of natural compounds on DNA methyltransferases and associated proteins. *J Breast Cancer* 2013; **16**: 23-31 [PMID: 23593078 DOI: 10.4048/jbc.2013.16.1.23]

82 **Stendell-Hollis NR**, Thomson CA, Thompson PA, Bea JW, Cussler EC, Hakim IA. Green tea improves metabolic biomarkers, not weight or body composition: a pilot study in overweight breast cancer survivors. *J Hum Nutr Diet* 2010; **23**: 590-600 [PMID: 20807303 DOI: 10.1111/j.1365-277X.2010.01078.x]

83 **Pan MH**, Lin CC, Lin JK, Chen WJ. Tea polyphenol (-)-epigallocatechin 3-gallate suppresses heregulin-beta1-induced fatty acid synthase expression in human breast cancer cells by inhibiting phosphatidylinositol 3-kinase/Akt and mitogen-activated protein kinase cascade signaling. *J Agric Food Chem* 2007; **55**: 5030-5037 [PMID: 17539658 DOI: 10.1021/jf070316r]

84 **Li M**, Wang J, Jing J, Hua H, Luo T, Xu L, Wang R, Liu D, Jiang Y. Synergistic promotion of breast cancer cells death by targeting molecular chaperone GRP78 and heat shock protein 70. *J Cell Mol Med* 2009; **13**: 4540-4550 [PMID: 19017364 DOI: 10.1111/j.1582-4934.2008.00575.x]

85 **Wang J**, Yin Y, Hua H, Li M, Luo T, Xu L, Wang R, Liu D, Zhang Y, Jiang Y. Blockade of GRP78 sensitizes breast cancer cells to microtubules-interfering agents that induce the unfolded protein response. *J Cell Mol Med* 2009; **13**: 3888-3897 [PMID: 19674193 DOI: 10.1111/j.1582-4934.2009.00873.x]

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