

Green tea mechanism of action in fighting different types of cancer

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ABSTRACT

Eat and drink natural to fight cancer. Natural products are important therapeutic effects with low toxicity, and could be used in cancer chemoprevention. This is the most important healthy lifestyle behaviors in the 21 century. More than half patients use vitamins or herbs concurrently with conventional anticancer treatment. Flavonoids or polyphenols existing in vegetables, fruits and beverages are known by their antioxidant properties and considered as anti-cancer agents. Examples of these include green tea. Green tea composed of flavonoid compounds with phenolic structures. These phytochemicals are highly reactive with other compounds, such as reactive oxygen species and biologic macromolecules, to neutralize free radicals or initiate biological effects. Phenolic phytochemicals with promising properties to benefit human health includes a group of polyphenol compounds, called catechins, found in green tea. This article summarizes the findings of studies using green tea polyphenols as chemopreventive and discusses the possible mechanisms of action in fighting different types of cancer.

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Key words: *Green tea, epigallocatechin-3-gallate, mechanism of action, antioxidant, cancer fighting.*

Introduction

Tea is the most popular beverage containing a large number of bioactive compounds, including catechins, flavonols, lignans, and phenolic acids. There is a positive relationship between tea consumption and beneficial health effects. Green tea is known to contain high quantities of several polyphenolic components which have antioxidants, antimutagenic and anticlastogenic effects (Seeram et al., 2006). Green tea (*Camellia sinensis*) extract contains a number of catechins, including epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-gallate (ECG), epicatechin (EC), and catechin (C) as reported by Fung et al. (2013). Graham (1992) delineated that fresh tea leaf is unusually rich in the flavanol group of polyphenols known as catechins which may constitute up to 30% of the dry leaf weight. Flavonoids can be sub-classified into flavones, flavanols, flavanones, catechins, anthocyanidins and isoflavanoids. The consumption of these compounds appears to promote good health. Green tea composed of other polyphenols such as chlorogenic acid, coumarylquinic acid, and one unique to tea, theogallin (3-galloylquinic acid). Caffeine is present at an average level of 3% along with very small amounts of the other common methylxanthines, theobromine and theophylline. The amino acid theanine (5-N-ethylglutamine) is also unique to tea. According to its chemical structure, EGCG is often classified as an antioxidant (Valenti et al., 2013). Green tea has attracted significant attention recently, both in the scientific and in consumer communities for its health benefits for a variety of diseases associated with oxidative stress such as cancer, cardiovascular, and neurodegenerative diseases (Roy et al., 2001). The beneficial effects of green tea are attributed to the antioxidant properties of the polyphenolic compounds; showing anti-inflammatory, anti-allergenic, antibacterial, and antiviral properties (Braicu et al., 2013), as well as antimutagenic activity (Kuroda & Hara, 1999).

Mechanism of Action

EGCG is the most abundant component in the green tea; and it has been extensively studied for its beneficial health effects as a nutraceutical agent (Kim S et al., 2014).

Oral Cancer

Oral cancer is a serious and growing issue in many countries. Oral and pharyngeal cancer, together, considered as the sixth most common cancer in the world (Siegel et al., 2012). Tea consumption may have a protective effect on oral cancer, especially green tea. Tao et al. (2013) showed that EGCG treatment increased the production of mitochondrial hydrogen peroxide (H₂O₂) in SCC-25 cells (0-6 h) before the induction of apoptosis. Subsequently, an opening of the mitochondrial transition pore and a decrease in mitochondrial membrane potential were observed. The mitochondria-

specific antioxidant, MitoTEMPO, reduced these effects. HGF-1 human gingival fibroblasts were resistant to EGCG ($IC_{50} > 200 \mu M$) and EGCG-induced reactive oxygen species (ROS). EGCG induced differential expression of genes related to antioxidant defense in oral cancer cells and gingival fibroblasts: metallothionein, superoxide dismutase, and thioredoxin reductase were downregulated in SCC-25 cells, but upregulated in HGF-1 cells. The authors conclude that induction of mitochondrial ROS and mitochondrial dysfunction by EGCG play a role in the inhibition of oral cancer, and that gingival fibroblasts are spared from these effects in part because of a selective induction of antioxidant responsive genes. Elattar & Virji (2000) evaluated the effect of three major tea constituents, EGCG, ECG, and EGC on the cell growth and DNA synthesis of human oral squamous carcinoma cell line SCC-25. These three compounds caused dose-dependent inhibition in both cell growth and DNA synthesis. A study by Masuda et al. (2002) has also demonstrated that treatment with EGCG induced cell cycle arrest at G1 phase due to decrease of cyclin D1 expression, increases of p21Cip1 and p27Kip1 expression, and reduction of hyper-phosphorylated form of pRB. Liu et al. (2011) have found that green tea extract and EGCG inhibited cell growth in three squamous cell lines (CAL-27, SCC-25, and KB) via S and G2/M phase cell cycle arrest. Results from Pathway Array assessment of 107 proteins indicated that major signaling pathways affected by green tea extract and EGCG were epidermal growth factor receptor (EGFR), which in turn affected cell cycle related networks. Weisburg et al. (2004) have also reported that the anti-proliferative effect of green tea polyphenols and EGCG, was more sensitive in oral cancer cell lines (CAL27, HSC-2, and HSG1) than normal fibroblasts (GN56 and HGF-1). EGCG treatment caused generation of H_2O_2 , one of major ROS. The results from assessment of cytotoxicity of a green tea polyphenol CG in cell lines derived from human oral cavity indicated that CG selectively induced cell death in favor of cancer cells (Babich et al., 2007). Further study indicated that cytotoxicity of CG in cancer cells was due to its capability of inducing H_2O_2 generation. EGCG showed a capacity in reduction of cell growth, induction of apoptosis, and inhibition of angiogenesis in oral cancer cell lines (Ko et al., 2007). Again, Chen et al. (2011) delineated that EGCG treatment in oral squamous SCC-9 cells blocked cell invasion via a reduced expression of matrix metalloproteinase-2 (MMP-2) and urokinase type plasminogen activator (uPA). EGCG exerted an inhibitory effect on cell migration, motility spread, and adhesion. EGCG inhibited phospho-focal adhesion kinase (p-FAK), p-Src, snail-1, and vimentin, indicating the anti-EMT effect of EGCG in oral squamous cell carcinoma. While, Kato et al. (2008) reported that RECK is a tumor suppressor gene that negatively regulates MMPs and inhibits tumor invasion, angiogenesis, and metastasis. The treatment of oral cancer cells with EGCG partially reversed the hypermethylation status of the RECK gene and significantly enhanced the expression level of RECK mRNA, leading to reduced MMP-2 and MMP-9 expressions.

Lung Cancer

It is one of the cancers that have the highest occurrence and the highest mortality rate, and it is of great interest to identify ways to prevent its incidence. Green tea is a promising chemopreventive agent for lung cancer. RNA-seq analysis revealed that Polyphenon E-treated cells shared 293 commonly down-regulated genes within TAM67 expressing H1299 cells, and by analysis of limited Chip-seq data, over 10% of the down-regulated genes contain a direct AP-1 binding site, indicating that Polyphenon E elicits chemopreventive activity by regulating AP-1 target genes. Conditional TAM67 expressing transgenic mice and NSCLC cell lines were used to further confirm that the chemopreventive activity of green tea is AP-1 dependent. Polyphenon E lost its chemopreventive function both in vitro and in vivo when AP-1 was inhibited, indicating that AP-1 inhibition is a major pathway through which green tea exhibits chemopreventive effects (Pan et al., 2014). Rats given 0.3% solution of tea polyphenols (equivalent to 1.2% of green tea) in drinking water. From 4 weeks to 16 weeks after carcinogen treatment, hyperplasia, cell hyper-proliferation, heterogeneity were observed in the bronchial epithelium. Tea polyphenols treatment significantly alleviated the bronchial epithelial lesions. At the same time, tea polyphenols treatment enhanced p53 expression, but reduced Bcl-2 expression. These results indicated that tea polyphenols may have preventive effect against lung pre-neoplasm lesions, possibly through up-regulating of the expression of some critical genes such as p53 and Bcl-2 (Gu, Q et al., 2013). Another pathway that inhibit the proliferation of lung cancer is microRNAs (miRs); which are a class of 21–24 nucleotide small non-coding RNAs and play critical roles throughout cellular development and regulation (Zhong et al. 2012). Emerging evidence demonstrates that tea catechins influence the expression of miRs in human cancer cells to inhibit tumorigenesis. Both let-7a-1 and let-7g were detected in the human lung cancer cells treated with tea catechins. The cell viability and cell cycle were analyzed after tea catechins treatment. In the present study, we found that tea catechins upregulated the tumor-suppressor miRs, let-7a-1 and let-7g, in lung cancer cell lines. The upregulation of let-7a/7g repressed the expression of their targets, C-MYC and the regulatory protein of LIN-28, at the mRNA and protein levels. Moreover, the cell growth assay indicated that tea catechins significantly inhibited cell proliferation, and the flow cytometric analysis revealed an increase in the number of cells in the G2/M phase and a decrease in the number of cells in the S phase after treatment with tea catechins. These observations suggest that green tea catechins mediate the inhibition of proliferation of lung cancer cells through the let-7 signaling pathway. Ma et al. (2014), reported that EGCG had a profound antiproliferative effect on human lung cancer cells. EGCG inhibited anchorage-independent growth and induced cell cycle G0/G1 phase arrest. The mechanism underlying EGCG antitumor potency was mainly dependent on suppression of the EGFR signaling pathway. Short-term EGCG exposure substantially decreased EGF-induced EGFR, AKT and ERK1/2 activation. Moreover, long-term EGCG treatment not only inhibited total and membranous EGFR expression, but also markedly attenuated EGFR nuclear localization and expression of the downstream target gene cyclin D1, indicating that EGCG treatment suppressed EGFR transactivation. Additionally,

knockdown of EGFR in lung cancer cells decreased their sensitivity to EGCG. Thus, inhibition of the EGFR signaling pathway may partly contribute to the anticancer activity of EGCG.

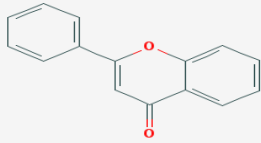
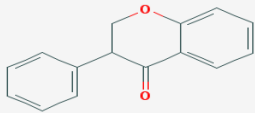
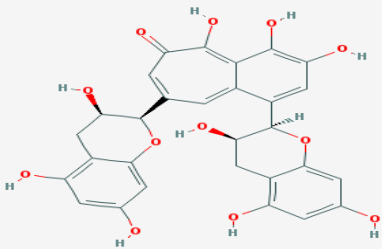
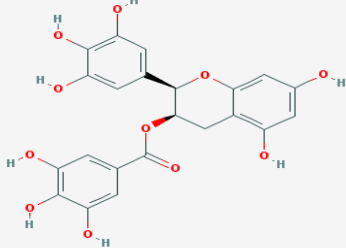
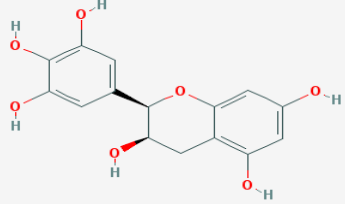
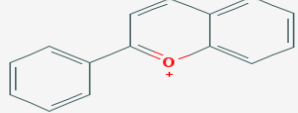
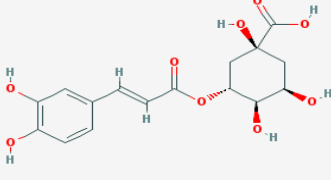
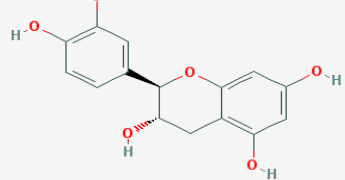
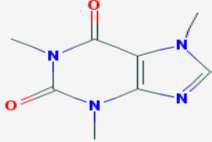
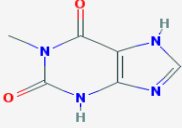
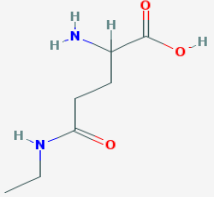
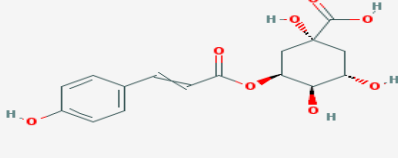
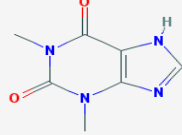
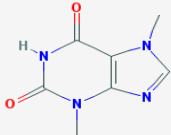
		
Flavone, CID 10680	Isoflavanone, CID 160767	Theaflavin, CID 114777
		
(-)-Epigallocatechin gallate, CID 65064	Galocatechol Also known as: (-)-Epigallocatechin, CID 72277	Anthocyanins (Leucoanthocynidines), CID 145858
		
Chlorogenic Acid, CID 1794427	Catechin, CID 9064	Caffeine, CID 2519
		
1-methylxanthine, CID 80220	n-ethylglutamine, DL-Theanine, CID 228398	Coumaroylquinic acid, CID 57351087
		
Theophylline, CID 2153	Theobromine, CID 5429	

Figure 1. Chemical formula of some components from tea

In this review, the mechanism of green tea and its constituent in fighting different types of cancer will be discussed.

Colon/Colorectal Cancers

Colon cancer is the second leading cause of cancer deaths, while; colorectal cancer is the third most common cancer worldwide and the third leading cause of cancer mortality in many countries (Parkin et al., 2006). Consumption of herbal tea (black and green tea) was associated with reduced risk of distal colon cancer (Green et al., 2014). Epigenetic gene silencing involving DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) plays an important role in the progression of colon cancer. Moseley et al. (2013) found that the sensitivity of colon cancer cells to methylation plays a role in its response to alternative therapy involving the GTPs and EGCG. HDAC and DNMT protein expression were reduced when methylation-sensitive HCT 116 human colon cancer cells was treated with EGCG, but was relatively stable in the HT-29 cell line. This decrease in expression may be partially explained by our finding that DNMT3A and HDAC3 are degraded in the methylation-sensitive colon cancer cells in part by inhibiting their association with the E3 ubiquitin ligase, UHRF1. Saldanha et al. (2014), investigated the role of the combinatorial effects of EGCG, a predominant polyphenol in green tea, and sodium butyrate (NaB), a dietary microbial fermentation product of fiber, in the regulation of survivin, which is an overexpressed anti-apoptotic protein in colon cancer cells. For the first time, our study showed that the combination treatment induced apoptosis and cell cycle arrest in RKO, HCT-116 and HT-29 colorectal cancer cells. This was found to be regulated by the decrease in HDAC1, DNMT1, survivin and HDAC activity in all three cell lines. A G2/M arrest was observed for RKO and HCT-116 cells, and G1 arrest for HT-29 colorectal cancer cells for combinatorial treatment. Further experimentation of the molecular mechanisms in RKO colorectal cancer cells revealed a p53-dependent induction of p21 and an increase in nuclear factor kappa B (NF- κ B)-p65. An increase in double strand breaks as determined by gamma-H2A histone family member X (γ -H2AX) protein levels and induction of histone H3 hyperacetylation was also observed with combination treatment. Further, we observed a decrease in global CpG methylation. These findings suggest that at low and physiologically achievable concentrations, combinatorial EGCG and NaB are effective in promoting apoptosis, inducing cell cycle arrest and DNA-damage in colorectal cancer cells. EGCG inhibited Erk-1 and Erk-2 activation in a dose-dependent manner in vitro on the growth of HT29 cells (Jung et al., 2001). However, other tea catechins such as EGC, ECG, and EC did not affect Erk-1 or Erk-2 activation at a concentration of 30 μ M. In the in vivo studies, athymic BALB/c nude mice were inoculated subcutaneously with HT29 cells and treated with daily intraperitoneal injections of EC (negative control) or EGCG at 1.5 mg day/mouse, starting 2 days after tumour cell inoculation. Treatment with EGCG inhibited tumour growth, microvessel density, and tumour cell proliferation and increased tumour cell apoptosis and endothelial cell apoptosis relative to the control condition. EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the induction of vascular endothelial growth factor (VEGF).

Hepatic Cancer

Green tea polyphenols (GTPs) have been proposed as promising candidates for chemoprevention. However, GTPs levels are maintained relatively low in the blood and are chemically-unstable. Lipid-soluble tea polyphenols (LTPs) are products of modified GTPs with ester linkage with fatty acids. Oral administration of LTPs (40, and 400 mg/kg/day) decreased the area and number of placental glutathione S-transferase-positive foci in liver samples of DEN-treated rats. Furthermore, LTPs counteracted DEN-induced fibrosis formation in liver. Immunohistochemical staining of rat liver showed that LTPs inhibited DEN-mediated elevations in numbers of cells positive for PCNA and 8-OHdG. LTPs exert a chemo-preventive effect against precancerous lesions through inhibition of cellular proliferation and DNA damage in a rat liver model (Shen et al., 2014). EGCG is a major polyphenol in green tea that has been shown to have anti-inflammatory, anti-cancer, anti-steatotic effects on the liver. EGCG inhibited cell proliferation and induced apoptosis. EGCG dephosphorylated constitutively activated Akt and increased the activation of p38. EGCG also decreased the expression of VEGF-receptor 2. EGCG suppressed angiogenesis and induced apoptosis in liver metastases without associated body weight loss or hepatotoxicity. Furthermore, the liver metastatic area was significantly reduced by EGCG administration (Maruyama et al., 2014). Autophagy also mediates similar effects; however, it is not currently known whether EGCG can regulate hepatic autophagy. Here, we show that EGCG increases hepatic autophagy by promoting the formation of autophagosomes, increasing lysosomal acidification, and stimulating autophagic flux in hepatic cells and in vivo. EGCG also increases phosphorylation of AMPK, one of the major regulators of autophagy. This may contribute to its beneficial effects in reducing hepato-steatosis and potentially some other pathological liver conditions (Zhou et al., 2014).

Prostate Cancer

Cancer of the prostate gland is the most common malignancy in males and its prevention is a crucial medical challenge especially in the developed countries. Even with successful treatment some patients are left with devastating unwanted side effects such as impotence and difficulties with urination. Wang, P. et al. (2014) reported that of GTPs administered to severe combined immunodeficiency (SCID) mice injected with Androgen-sensitive LAPC-4 prostate cancer cells. the concentration of GTPs in brewed tea as drinking water was 0.07% and methylation inhibitor quercetin (Q) was supplemented in diet at 0.2% or 0.4%. After 6-weeks of intervention tumor growth was inhibited by 3% (0.2% Q), 15% (0.4% Q), 21% (GT), 28% (GT+0.2% Q) and 45% (GT+0.4% Q) compared to control. The concentration of non-methylated GTPs was significantly increased in tumor tissue with GT+0.4% Q treatment compared to GT alone, and was associated with a decreased protein expression of catechol-O-methyltransferase and multidrug resistance-

associated protein (MRP)-1. The combination treatment was also associated with a significant increase in the inhibition of proliferation, androgen receptor and phosphatidylinositol 3-kinase/Akt signaling, and stimulation of apoptosis. Therefore, chemoprevention to reduce the risk and inhibit the progression of prostate cancer may be an effective approach to reducing disease burden. We investigated the safety and efficacy of Polyphenon E (200, 500, 1,000 mg/kg/day), a green tea extract, in reducing the progression of prostate cancer in TRAMP and C57BL/6J mice. The number and size of tumors in treated TRAMP mice were significantly decreased compared to untreated animals. In untreated 32 weeks old TRAMP mice, prostate carcinoma metastasis to distant sites was observed in 100% of mice (8/8), compared to 13% of mice (2/16) treated with high dose Polyphenon E during the same period. Further, Polyphenon E treatment significantly inhibited metastasis in TRAMP mice in a dose-dependent manner ($P=0.0003$). Long-term (32 weeks) treatment with Polyphenon E was safe and well tolerated with no evidence of toxicity in C57BL/6J mice (Kim, S. et al., 2014). Polyphenon E is an effective chemopreventive agent in preventing the progression of prostate cancer to metastasis in TRAMP mice. Polyphenon E showed no toxicity in these mouse models. Impact: Our findings provide additional evidence for the safety and chemopreventive effect of Polyphenon E in preventing progression of prostate cancer. Proteasome target proteins include tumor suppressor proteins, p21, p27, I κ B α , and Bax, and it is considered an important target for cancer prevention and therapy (Connors et al., 2012). GTCs inhibit proteasome activity in assays that used purified 20S proteasome, whole cell extract, and intact, living cells. After drinking the equivalent of 5 cups of green tea, human plasma levels reach a maximum of 1.6 μ M, 0.6 μ M, and 0.6 μ M of EGC, EGCG, and EC, respectively (Yang, 1999). Treating prostate cancer cell lines with similar levels of EGCG (0–0.5 μ M), resulted in the inhibition of chymotrypsin-like proteasome activity in LNCaP, PC-3, and DU-145 prostate cancer cells. This inhibition resulted in the accumulation of the proteasome targets, cyclin-dependent kinase inhibitor (CKI), p27, and the NF κ B inhibitor, I κ B α , and caused cell cycle arrest (Nam et al., 2001). Treatment of prostate cancer cells with synthetic GTCs yielded similar results and induced the expression of the proteasome target, Bax, and cleavage of caspase-3 and PARP (Smith et al., 2002). GTC-induced inhibition of proteasome activity, however, has not been directly confirmed in rodent models or human studies. Another study by Mitterberger et al. (2007) showed that tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL/Apo2L) is a part of the extrinsic pathway of apoptosis and this death receptor pathway is often resistant in the androgen sensitive LNCaP cells (Sanlioglu et al., 2007). Recently, a synergistic effect of EGCG (20 μ M) when used in combination with TRAIL (100 ng/ml) was observed and resulted in three events: upregulation of poly(ADP-ribose) polymerase cleavage and modulation of pro- and anti-apoptotic Bcl-2 family of proteins, modulation of TRAIL R1 and Fas-associated death domain and FLICE-inhibitory protein proteins leading to decreased invasion and migration of LNCaP cells (Siddiqui et al., 2008). Further evaluation of EGCG in combination with TRAIL revealed decreased invasion and migration as seen through inhibition of VEGF, uPA, angiopoietin 1 and 2, MMP2,-3, -9 and upregulation of TIMP-1.

Breast cancer

This type 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 (Rebecca & Jemal, 2013). Regular green tea intake has been associated with an inverse risk of breast cancer. Postmenopausal women with ductal carcinoma in situ (DCIS) or stage I or II breast cancer took green tea capsules (940 mg/day) for an average of 35 days prior to surgery. Cell proliferation (Ki-67) levels declined in both benign and malignant cell components in the green tea group; the decline in Ki-67 positivity in malignant cells was not statistically significant but was statistically significant in benign cells. There was a statistically significant difference in the change in Ki-67 in benign cells between the green tea and the no green tea groups (Yu et al., 2013). A further study suggested that the effect of EGCG on tumour size was mediated by the inhibition of hypoxia-inducible factor 1 α (HIF-1 α) and nuclear factor κ B (NF- κ B) activation as well as vascular endothelial growth factor (VEGF) expression (Gu JW et al., 2013). Another study demonstrated that EGCG significantly reduced tumor volume in a xenograft mouse model developed using stem-like SUM-149 breast cancer cells (Mineva et al., 2013). One recent study by Deb et al. (2015) delineated that GTPs and its major constituent, EGCG mediate epigenetic induction of TIMP-3 levels and play a key role in suppressing invasiveness and gelatinolytic activity of MMP-2 and MMP-9 in breast cancer cells. Treatment of MCF-7 and MDA-MB-231 breast cancer cells with 20 μ M EGCG and 10 μ g/mL GTP for 72 h significantly induces TIMP-3 mRNA and protein levels. Interestingly, investigations into the molecular mechanism revealed that TIMP-3 repression in breast cancer cells is mediated by epigenetic silencing mechanism(s) involving increased activity of the enhancer of zeste homolog 2 (EZH2) and class I histone deacetylases (HDACs), independent of promoter DNA hypermethylation. Treatment of breast cancer cells with GTP and EGCG significantly reduced EZH2 and class I HDAC protein levels. Furthermore, transcriptional activation of TIMP-3 was found to be associated with decreased EZH2 localization and H3K27 trimethylation enrichment at the TIMP-3 promoter with a concomitant increase in histone H3K9/18 acetylation. Our findings highlight TIMP-3 induction as a key epigenetic event modulated by GTPs in restoring the MMP:TIMP balance to delay breast cancer progression and invasion. Mocanu et al. (2014), demonstrated that EGCG flavonoids inhibit cell proliferation, by downregulation of ErbB1 and ErbB2 in mammary and epidermoid carcinoma cells, and its inhibitory effect on cell viability was mediated by the 67 kDa laminin receptor (67LR). Furthermore, EGCG decreased the homocustering of a lipid raft marker, glycosylphosphatidylinositol-anchored GFP, and it also reduced the co-localization between lipid rafts and 67LR. The authors concluded that the primary target of EGCG may be the lipid raft component of the plasma membrane followed by secondary changes in the expression of ErbB proteins.

Ovarian and Cervical Cancer

Ovarian cancer is the leading cause of death from gynecologic cancers in the world and is the fifth leading cause of cancer death among women. EGCG significantly inhibited the proliferation of OVCAR-3 cells in a time- and concentration-dependent manner. EGCG (100 µM) time-dependently increased the activity of p38, but not extracellular signal-regulated kinases 1/2. SB203580, a specific of mitogen-activated protein kinase-p38 (p38 MAPK) inhibitor, completely diminished EGCG-induced phosphorylation of p38 and partially blocked EGCG-inhibited OVCAR-3 cell proliferation. Furthermore, EGCG (0-100 µM) dose-dependently inhibited OVCAR-3 cell migration. The protein expression levels of MMP-2, but not MMP-9, were dose-dependently decreased following treatment with EGCG (0-100 µM) for 48 h; leading to inhibited OVCAR-3 cell proliferation and migration, potentially mediated via the activation of p38 MAPK and downregulation of the protein expression of MMP-2 (Wang, F. et al., 2014). It has been reported that EGCG can induce apoptosis in breast cancer cells, and EGCG can target cancer cells through a variety of mechanisms, including decreasing expression of hTERT, the major catalytic subunit of telomerase (Berletch et al., 2008).

Glioma Cancer

Glioma is a malignant tumor with high mortality and effective efforts are affordable to find therapy with no side effects for this type of cancer. Yokoyama et al. (2001) indicate that the green tea polyphenol EGCG can affect growth of gliomas. The antitumor effects of EGCG were heterogeneous in the 3 glioma cell lines. By MTT assay, U-373 MG and U-87 MG cells showed a higher sensitivity to EGCG than did C6 cells. The lower serum insulin-like growth factor-I (IGF-I) concentration improves the efficacy of chemotherapeutic drugs for the treatment of breast cancer. The treatment with EGCG resulted in IGF-1 inhibition in glioma cell lines. Following the same line, Li et al. (2014) reported that EGCG induced apoptosis in U251 glioma cells via the laminin receptor (molecular weight 67kDa) in a time- and dose-dependent manner, decreased their invasiveness and inhibited their proliferation. The mitogen-activated protein kinase pathway was shown to be involved in glioma cell apoptosis and proliferation. Furthermore, the mRNA levels of MMP-2 and MMP-9 were reduced after EGCG treatment.

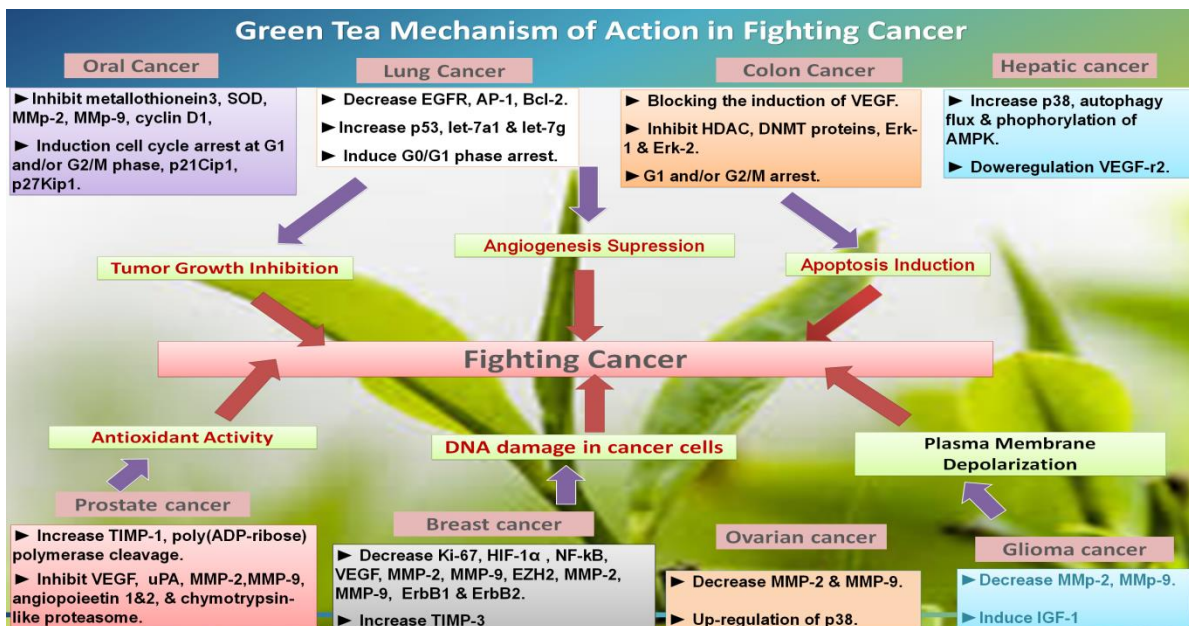


Figure 2. Diagram summarizes the mechanism of action of green tea in fighting different types of cancer.

Conclusion

This review summarizes the mechanisms of polyphenols against cancer in vitro, in vivo, and in clinical studies. The preventive effects of green tea for a number of cancer types have been demonstrated, including oral, colon, colorectal, lung, hepatic, prostate, breast, ovarian, and brain cancer. The proposed mechanisms of action include antioxidant effects, inhibition of growth-factor signaling, and enhancement of chemotherapy agents. Polyphenols are potentially useful for counteracting the DNA damage induced by oxidative stress agents (García-Rodríguez et al., 2013). EGCG functions as a pro-oxidant directly interacts with proteins and phospholipids in the plasma membrane depolarization and regulates signal transduction pathways, transcription factors, DNA methylation, mitochondrial function, cytochrome c release, and autophagy to exert many of its beneficial biological actions (Kim, H-S. et al., 2014). More recent findings suggest additional mechanisms of action for EGCG including interactions with plasma membrane proteins, activation of second messengers and modulation of metabolic enzymes (Zhnag et al., 2012); which are concentration-dependent. EGCG competitively inhibits the enzyme dihydrofolate reductase (DHFR). Studies revealed that EGCG levels found in tissue and blood samples of people who drank green tea were sufficient to bind DHFR, inhibit the growth of cells, and induce

apoptosis, and reduce tumor growth (Augustin et al., 2009). Another interesting property have been reported by Ahmad et al. (1997), who delineated that EGCG caused apoptosis only in malignant tumor cell lines and did not affect normal cells. These results suggest that EGCG inhibits cell proliferation in malignant, highly proliferative brain tumors, but has no effect on normal cells or benign tumor cells.

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