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# Green tea polyphenols: biology and therapeutic implications in cancer

**Sharmila Shankar, Suthakar Ganapathy, Rakesh K. Srivastava**

*Department of Biochemistry, University of Texas Health Science Center at Tyler, Tyler, Texas, USA 75703*

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## 1. ABSTRACT

Multiple lines of evidence, mostly from population-based studies, suggest that green tea consumption is associated with reduced risk of several human malignancies such as cancer and diabetes. Epigallocatechin-3-gallate (EGCG), a major polyphenol found in green tea, is a widely studied chemopreventive agent with potential anticancer activity. Green tea polyphenols inhibit angiogenesis and metastasis, and induce growth arrest and apoptosis through regulation of multiple signaling pathways. Specifically, EGCG regulates expression of VEGF, matrix metalloproteinases, uPA, IGF-1, EGFR, cell cycle regulatory proteins and inhibits NFκB, PI3-K/Akt, Ras/Raf/MAPK and AP-1 signaling pathways, thereby causing strong cancer chemopreventive effects. This review discusses the molecular mechanisms of green tea polyphenols and their therapeutic implications in cancer.

## 2. INTRODUCTION

Green tea is a popular beverage consumed widely in China, Japan and India, and is a rich source of flavanoids (1-3). Flavanoids are the low molecular weight compounds 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. Catechins are especially concentrated in green tea (*Camellia sinensis*) which account for 30-40% of the dry weight of the leaves. A polyphenolic constituent, (-)-epigallocatechin-3-gallate (EGCG), is the major and most effective chemopreventive agent in green tea. Epidemiologic and rodent carcinogenesis studies have provided evidence that green tea has chemopreventive effects for a wide range of malignancies (4-11). The consumption of green tea is associated with a lower risk of several types of cancer, including stomach, esophagus, prostate and lung (2, 3, 12, 13). It has also been reported that the quantity of green tea

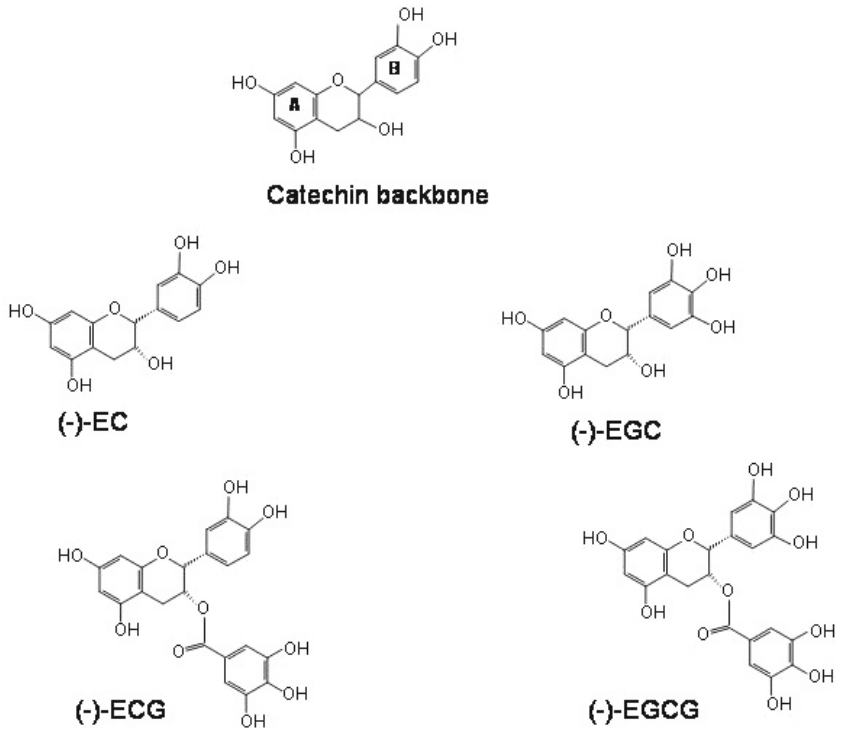


**Figure 1**. Structure of the major catechins found in green tea. The structures of catechin backbone, (-)-epicatechin, (EC); (-)-epicatechin-3-gallate, (ECG); (-)-epigallocatechin, (EGC); (+)-gallocatechin, (GC); and (+)-gallocatechin-3-gallate, (EGCG) are shown.

consumed plays an important role in reducing cancer risk and in delaying cancer outbreak and recurrence. It acts as an antioxidant, antiproliferative, antitumor, and anti-angiogenic agent, and thus a novel candidate for chemoprevention (2, 3, 13). Mechanistic studies have indicated that EGCG exerts various anticancer effects, including suppression of growth factor-mediated proliferation (6), inhibition of transformation (5), and repression of angiogenesis (8, 10). Tea and tea polyphenols have shown inhibitory activity during the initiation, promotion, and progression stages of carcinogenesis (9, 11). *In vitro*, tea polyphenols, especially EGCG, have been shown to cause growth inhibition and apoptosis in several human tumor cell lines, including melanoma, breast cancer, lung cancer, leukemia, and colon cancer (3, 13-16). The main objective of this review is to discuss the molecular mechanisms of green tea polyphenols and their therapeutic implications in cancer.

## 3. TEA POLYPHENOLS

EGCG is the major constituent found in green tea. Several other polyphenolic compounds found in lower abundance in green tea include (-)-epicatechin-3-gallate, (ECG); (-)-epigallocatechin, (EGC); (-)-epicatechin, (EC); (+)-gallocatechin, (GC); (+)-gallocatechin-3-gallate, (GCG) and catechin (Figure 1). Several *in vitro* and animal models suggest that green tea polyphenols inhibit a vast array of biomedically relevant molecular targets and disease related cellular processes (17, 18).

## 4. MECHANISMS OF ACTION

Green tea polyphenols induce growth arrest and apoptosis, and inhibit angiogenesis and metastasis through regulation of multiple signaling pathways. Specifically, EGCG regulates expression of Bcl-2 family members, VEGF, MMPs, uPA, IGF-1, EGFR, cell cycle inhibitors ($p21^{/WAF1/CIP1}$, and $p27^{/KIP1}$), and inhibits survival signaling pathways such as NFκB, PI3-K/Akt, and Ras/Raf/MAPK, thereby causing strong cancer chemopreventive effects (Figure 2). The molecular mechanisms of EGCG and related polyphenols are summarized below.

### 4.1. Bcl-2 family members

Recently, the Bcl-2 gene family has emerged as critical regulators of apoptosis in a variety of physiological and pathological processes (19, 20). Study of the mechanism of apoptosis by Bcl-2-related genes offers new possibilities for prevention and treatment of several human diseases (21, 22). Some of the proteins within this family, including Bcl-2 and Bcl-$X_L$ inhibit apoptosis, and others, such as Bcl-$X_S$, Bax and Bak, promote apoptosis (19, 20). Indeed, the ratio between these two subsets determines, in part, the susceptibility of cells to a death signal (23). Furthermore, these death-inducing proteins heterodimerize with members of the death-inhibitory family (19). The "BH-3-only protein" PUMA is an essential mediator of p53-dependent and -independent apoptosis *in vitro* and *in vivo* (24-26). This suggests that PUMA can bypass the p53 control mechanism of apoptosis *in vivo*, and thus enhance

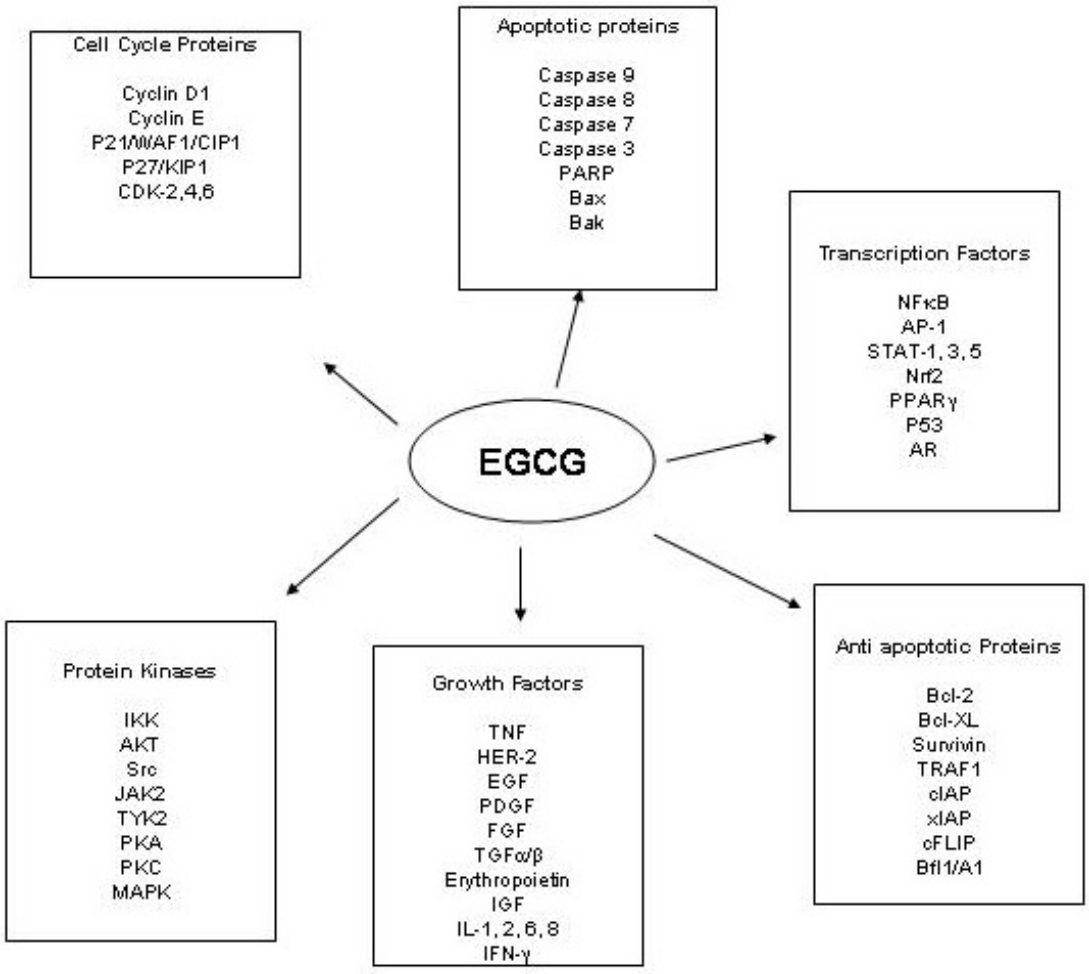


**Figure 2.** Molecular targets of green tea polyphenols. Green tea polyphenols exert their effect on multiple signaling pathways. They regulate cell cycle proteins (cyclin D1, cyclin E, $p21^{/WAF1/CIP1}$, $p27^{KIP1}$ and CDK-2/4/6), protein kinases (IKK, AKT, Src, JAK2, TYK2, MAPK, PKA and PKC), growth factors (EGF, HER-2, PDGF, FGF, TGF-α/β, Erythropoietin, IGF-I, IL-1/2/6/8, and IFNγ), transcription factors (NFκB, AP-1, STAT-1/3/5, Nrf2, PPAR, p53 and AR), proapoptotic proteins (caspases, PARP, Bax and Bak) and antiapoptotic proteins (Bcl-2, Bcl-$X_L$, survivin, cIAP1, xIAP, cFLIP, TRAF1 and Bfl1/A1).

the therapeutic potential of EGCG in cells harboring wild type and mutated p53. PUMA is likely to play a role in mediating cell death through the cytochrome c/Apaf-1-dependent pathway. We and others have shown that overexpression of Bcl-2 or Bcl-$X_L$ protects a wide variety of cell types from many death-inducing stimuli (27-33). We and others have shown that EGCG inhibits the expression of antiapoptotic proteins Bcl-2, Bcl-$X_L$ and induces expressions of proapoptotic proteins such as Bax, Bak, PUMA, Noxa and Bim, suggesting that the Bcl-2 family members play major roles in inducing cell growth and apoptosis (34-39).

**4.2. Matrix metalloproteinases**

Proteolytic degradation of components like collagen, proteoglycan, laminin, elastin and fibronectin in the extracellular matrix is considered to be the prerequisite for tumor invasion and metastasis. Matrix metalloproteinases (MMPs) can degrade essentially all of the protein components of the extracellular matrix (40, 41). In addition, these MMPs also substantially contribute to angiogenesis, differentiation, proliferation and apoptosis (40-42). Hence, MMPs are important regulators of tumor growth both at the primary site and in distant metastases and considered important targets for cancer therapy (43). Among the various types of MMPs, gelatinase A (MMP-2) and gelatinase B (MMP-9) seem to play an important role in tumor invasion and metastasis (44). The expression of MMPs is primarily regulated through AP-1 via mitogen activated protein kinase (MAPK) pathway (45, 46). Thus, MMPs and their regulatory pathways have been considered the promising targets for anticancer drugs and chemopreventive agents (47).

EGCG has been shown to inhibit metastasis of lung cancer cells by inhibiting MMP-9 (48). EGCG and

EGC inhibited Interleukin (IL)-1β-induced expression of the collagenases, MMP-1, MMP-3 and MMP-13, and the stromelysin in human tendon-derived fibroblasts, and had a smaller effect on MMP-2 mRNA expression, which was not stimulated by IL-1β (49). GTP and EGCG significantly inhibited the expression of VEGF, MMP-2 and MMP-9 in prostate cancer cells of TRAMP mice and in DU-145 cells, respectively (46, 50). EGCG inhibited the phorbol 12-myristate 13-acetate (PMA)-induced cell invasiveness and MMP-9 expression in human gastric cancer AGS cells (51). EGCG also abrogated the PMA-induced activation of ERK and JNK, which are upstream modulators of AP-1 (51). Overall, these results suggest that EGCG may exert at least part of its anti-invasive effect in several cancers by controlling MMP expression through the suppression of MAPK and AP-1 activation.

**4.3. RAS/MAP kinases**

The Ras proteins are small (21 kDa) GTP-binding, membrane-associated proteins (52). They are in their activated state when bound to GTP, and are inactivated by GTP hydrolysis. This intrinsic GTPase activity is enhanced by association with GTPase-activating protein (52). The Ras proteins transduce signals from ligand-activated tyrosine kinase receptors to downstream effectors (53). Activating mutations can impair GTP hydrolysis and lead to constitutively activated Ras that impacts the cellular phenotype (54). Oncogenic Ras can lead to cellular transformation (55), presumably by perturbing its signal transduction pathways. Ras regulates multiple signaling pathways (56). Three major groups of MAP kinases are found in mammalian cells: extracellular signal-regulated protein kinase (ERK) (57), p38 MAP kinase (58), and c-Jun N-terminal kinase (JNK) (59-61). MAP kinases regulate many cellular activities, which range from gene expression to mitosis, movement, metabolism, and apoptosis. These MAP kinases are activated by the dual phosphorylations of neighboring threonine and tyrosine residues in response to various extracellular stimuli (62, 63). Specifically, p38 and JNK have been implicated in stress-responsive signaling leading to the initiation of adaptive events such as gene expression, differentiation, metabolism, and apoptosis (59, 60, 64). ERKs are often activated by growth signals, such as epidermal growth factor (EGF) or platelet-derived growth factor (65).

EGCG induces JNK pathway which causes the release of cytochrome c and apoptosis in colon cancer cells (66). EGCG-induced JNK activation was blocked by the antioxidants glutathione and N-acetyl-l-cysteine, suggesting the involvement of oxidative stress in EGCG-induced apoptosis (66). EGCG-induces p57/KIP2 via the p38 MAPK signaling pathway in oral carcinoma cells (67). In p57-negative tumor cells, JNK signaling mediates EGCG-induced apoptosis, and exogenous expression of p57 suppresses EGCG-induced apoptosis via inhibition of JNK. Furthermore, restoration of p57 expression in tumor cells significantly reduced tumorigenicity in athymic mice, suggesting that p57 expression may be useful as a target for cancer therapies.

**4.4. PI3-kinase/AKT**

PTEN (phosphatase and tensin homolog deleted on chromosome 10, also called MMAC1 or TEP1) is a tumor suppressor gene identified on human chromosome 10q23 (68-70). PTEN is frequently deleted or mutated in a wide range of human cancers, including glioblastoma (71), melanoma (72), and prostate (73), breast (74), and endometrial cancers (75). Germ line PTEN mutations are present in patients with Cowden disease and Bannayan-Zonana syndrome (76, 77). Besides functioning as a tumor suppressor, PTEN is also essential for embryonic development (78-80). Phosphatidylinositol 3,4,5-trisphosphate ($PIP_3$) is a substrate of PTEN (81-83). Many tumor-associated missense mutations cluster around the phosphatase domain, and most remaining mutations are predicted to truncate the protein due to nonsense or frameshift mutations (68, 69, 84), suggesting that the phosphatase activity of PTEN plays important roles in PTEN function. Recent evidence demonstrates the ability of PTEN to directly dephosphorylate position D3 of $PIP_3$ (81). PTEN increases sensitivity to cell death in response to several apoptotic stimuli by negatively regulating the PI3K/Akt pathway (82). In addition to its role in regulating the PI3K/Akt cell survival pathway, PTEN also inhibits growth factor-induced Shc phosphorylation and suppresses the MAP kinase signaling pathway (85), suggesting that PTEN has roles in independent signaling pathways. We have shown that PTEN overexpression in human prostate cancer cells induces apoptosis, regardless of the presence of endogenous PTEN, and Akt was identified as a key molecule in this effect (86).

Akt is one of the most frequently activated protein kinases in human cancer (87). Hyperactivation of Akt is associated with resistance to apoptosis, increased cell growth, cell proliferation, and cellular energy metabolism (87, 88). Thus, Akt contributes to tumor growth and progression by promoting cell invasiveness and angiogenesis (86, 89-94). Overexpression of Akt has been reported in a variety of human cancers, and cells expressing elevated levels of Akt are less sensitive to apoptosis stimuli (95-98). Mammalian cells express three highly homologous Akt isoforms (Akt-1-3) that are encoded by separate genes and share over 80% amino acid sequence identity. Upon activation, growth factor receptors activate the catalytic p110 subunit of PI3K via recruitment of the corresponding p85 regulatory subunit or via ras activation, which can directly activate p110. p110 then phosphorylates phosphoinositides (PI) at the D3 position of the inositol ring to generate PI (3,4,5) P3 (PIP3). The rate limiting steps in Akt activation is the binding of PIP3 to the PH domain of Akt and subsequent translocation of Akt to the plasma membrane. Akt is then phosphorylated by PI3K-dependent kinase-1 (PDK1) at a threonine residue in the catalytic domain (Thr308), and by another kinase PDK2 at a serine residue (Ser473) in the carboxy-terminal hydrophobic motif. Phosphorylation at both sites is required for full activation of Akt. Antagonizing PI3K activity negatively regulates Akt activity. Once activated, however, Akt exerts antiapoptotic effects through phosphorylation of substrates such as Bad (99, 100) and caspase-9 (101) that directly regulate the apoptotic

machinery, or human telomerase reverse transcriptase subunit (102), forkhead transcription family members (103, 104) and IB kinases (105) that indirectly inhibit apoptosis (106).

EGCG has been shown to inhibit cell growth and proliferation by inhibiting PI-3K/Akt pathway in breast, bladder, prostate, and cervical cancers (35, 107-109). Green tea extract and EGCG inhibited serum-induced HIF-1α protein and VEGF expression by interfering with the PI3-K/Akt/mammalian target of rapamycin signaling pathways in human cervical carcinoma and hepatoma cells (110). EGCG inhibited tyrosine phosphorylation of PDGFβ-receptor and downstream activation of ERK and PI3-K/Akt pathways in pancreatic cancer cells (111). Treatment with EGCG inhibited the constitutive activation of the EGFR, Stat3, and Akt in YCU-H891 head and neck squamous cell carcinoma (HNSCC) and MDA-MB-231 breast carcinoma cell lines (112). Furthermore, EGCG inhibited PI-3K/Akt activation that, in turn, resulted in modulation of Bcl-2 family proteins, leading to enhanced apoptosis of bladder cancer T24 cells (35). These findings suggest that PI3-K/Akt pathway could be a major target for chemoprevention.

**4.5. Cyclooxygenases**

Cyclooxygenase (COX) is an enzyme that is responsible for formation of important biological mediators called prostanoids (including prostaglandins, prostacyclin and thromboxane). Pharmacological inhibition of COX can provide relief from the symptoms of inflammation and pain. Currently three COX isoenzymes are known - COX-1, COX-2 and COX-3. COX-3 is a splice variant of COX-1 which retains intron one and has a frameshift mutation (113). Different tissues express varying levels of COX-1 and COX-2. Although both enzymes act basically in the same fashion, selective inhibition can make a difference in terms of side-effects. COX-1 is considered a constitutive enzyme, being found in most mammalian cells. More recently it has been shown to be upregulated in various carcinomas and to have a central role in tumorigenesis. COX-2, on the other hand, is undetectable in most normal tissues. It is an inducible enzyme, becoming abundant in activated macrophages and other cells at sites of inflammation.

EGCG inhibits COX-2 without affecting COX-1 expression at both the mRNA and protein levels, in androgen-sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells (114). EGCG inhibited the expression of COX-2 and the production of PGE-2 (115). The effect of EGCG on COX-2 expression resulted in decreased COX-2 promoter activity via inhibition of NF□B activation (116). EGCG also promoted rapid mRNA decay mediated through the COX-2 3'untranslated region (3'UTR). In conclusion, these data suggest that inhibition of COX-2 is a mechanism for the anti-proliferative effect of green tea, and emphasizes the role of green tea polyphenols in cancer prevention and treatment.

EGCG treatment to colon cancer cells resulted in a strong activation of AMPK (AMP-activated protein kinase) and an inhibition of COX-2 expression (117). The decreased COX-2 expression as well as prostaglandin E2 secretion by EGCG was completely abolished by inhibiting AMPK by an AMPK inhibitor, compound C. In another study, cotreatment of lung cancer cells with EGCG plus celecoxib (a cyclooxygenase-2 inhibitor) strongly induced the expression of GADD153 (growth arrest and DNA damage-inducible 153), while neither EGCG nor celecoxib alone was effective (118). However, cotreatment did not induce expression of other apoptosis related genes, $p21^{/WAF1/CIP1}$ and GADD45. Upregulation of GADD153 by cotreatment with EGCG plus celecoxib correlated with induction of apoptosis.

**4.6. Epidermal growth factor**

The epidermal growth factor receptor (EGFR) belongs to a family of receptor tyrosine kinases in mammals which is composed of four members: EGFR/ERB1, ERB2/ HER2/neu, ERB3, and ERB4 (119, 120). EGFR is an 1186 amino acid residue transmembrane glycoprotein (121). The binding of specific polypeptide ligands results in phosphorylation of multiple tyrosine residues in the COOH-terminal tail, triggering the cellular signaling pathway that regulates fundamental cellular processes such as proliferation, migration, differentiation and survival. Although the ERB family is regarded as the prototypical group of the receptor tyrosine kinase (RTK) family, an important defining feature of the ERB network is that two members of the family, ERB2 and ERB3, are non-autonomous. ERB2 lacks the capacity to interact with a growth-factor ligand, whereas the kinase activity of ERB3 is defective. Despite this lack of autonomy, both ERB2 and ERB3 form heterodimeric complexes with other ERB receptors that are capable of generating potent cellular signals. EGFR is over expressed in many types of tumor cells, such as breast, brain, bladder, lung, gastric, head & neck, cervix, ovary and endometrium (122).

EGCG caused a decrease in the phosphorylated forms of EGFR and HER2 proteins, and subsequently caused a decrease in the phosphorylated forms of the ERK and Akt proteins (123). Similar effects of these compounds were seen when the cells were stimulated with TGFα. Reporter assays indicated that EGCG inhibited the transcriptional activity of the AP-1, c-fos, NFκB, and cyclin D1 promoters (123). In head and neck squamous cell carcinoma, EGCG inhibited phosphorylation of the EGFR, Stat3 and ERK proteins, and also inhibited basal and TGFβ-stimulated c-fos and cyclin D1 promoter activity (124). In cervical cancer, EGCG inhibited EGF-dependent activation of EGFR, and EGFR-dependent activation of the ERK1/2 (107). EGCG also inhibited EGFR-dependent AKT activity. The EGCG-dependent reduction in ERK and AKT activity is associated with reduced phosphorylation of downstream substrates, including p90RSK, FKHR, and BAD. In another study, EGCG markedly inhibited EGF-induced cell transformation of mouse epidermal JB6 Cl 41 cells (125), and EGF-induced activation of AP-1, and PI3K (125). Overall, these studies demonstrate that targeting the EGF signaling pathway by EGCG may be an effective strategy for prevention and treatment of cancers.

### 4.7. Insulin-like growth factors

The insulin-like growth factors (IGFs) play an important role in normal growth and development (126). Evidence suggests they may also regulate the growth of several cancer cell types (126-131). This regulation is mediated by interactions between the receptors and ligands. There is now ample evidence to suggest that these interactions are also influenced by extracellular IGF binding proteins (IGFBPs). Six different IGFBPs have been cloned. Some species may act to inhibit the mitogenic effects of the IGFs. Furthermore, inhibitory binding proteins could be used as neutralizers of IGF action. The insulin-like growth factor (IGF)-I receptor (IGF-IR) is a tyrosine kinase receptor that is activated by the binding of secreted growth factors, IGF-I or IGF-II. The IGF-IR is a heterotetrameric transmembrane glycoprotein with two identical α-subunits, which are responsible for ligand binding, and two identical β-subunits, which contain a juxtamembrane domain, an ATP binding pocket, an intracellular tyrosine kinase domain, and COOH terminus, and are joined by disulfide bridges (132). On ligand interaction with the IGF-IRα subunit, residues in the tyrosine kinase domain of the ß-subunit are autophosphorylated. Additional phosphorylation sites adjacent to these tyrosine residues can serve as a docking site for the adaptor protein, insulin receptor substrate-1 (IRS-1), which mediates activity through the regulatory subunits of PI-3K. The receptor can also recruit the Src homology-2 domain containing transforming protein, leading to activation of the Ras/Raf/ERK pathway (126, 133).

EGCG is a highly potent inhibitor of IGF-IR tyrosine kinase activity and malignant cell growth (134). Furthermore, IGF-IR autophosphorylation in the presence of increasing ATP concentrations was unaltered by EGCG treatment. Thus, EGCG can block IGF-IR kinase activity and phosphorylation of its downstream targets, resulting in an inhibition of IGF-IR-mediated cell proliferation and transformation. Green tea polyphenols inhibited IGF-1 and IGFBP-3 in TRAMP mice (135). Neutralization of IGF-I with an antihuman IGF-I antibody reduced viability of the human glioblastoma cell lines (136), suggesting that EGCG has an inhibitory effect on malignant brain tumors, and IGF-I may be involved in the effects of EGCG. Overall, these studies demonstrate that targeting the IGF-I signaling pathway by EGCG may be useful for prevention and treatment of cancer.

### 4.8. Transcription factors

#### 4.8.1. NFκB

Nuclear factor-κB (NFκB) is a family of closely related protein dimers that bind a common sequence motif in DNA called the κB site, which was originally discoved in B cells. Under resting conditions, NFκB dimers reside in the cytoplasm. NFκB is activated by free radicals, inflammatory stimuli, cytokines, carcinogens, tumor promoters, endotoxins -radiation, ultraviolet light and X-rays. Upon activation, it is translocated to the nucleus, where it induces the expression of more than 200 genes that have been shown to suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis, chemo-resistance, radio-resistance and inflammation. Many of the target genes that are activated are critical to the establishment of the early and late stages of aggressive cancers including expression of cyclin D1, Bcl-2, Bcl-$X_L$, MMPs and VEGF.

Phosphorylation of $I_KB$ by $I_KB$ kinase causes ubiquitination and degradation of IκB, thus releasing NFκB that then translocates to the nucleus. Phosphorylation and activation of IκB kinase is controlled by and NFκB inducing kinases and there is crosstalk between activation of the MAPK, ERK pathway and the NFκB-inducing kinase/IκB kinase/NFκB pathway. EGCG has been shown to inhibit NFκB activity in human colon, prostate cancer cells (137-143). Treatment of normal human epidermal keratinocytes with EGCG was found to inhibit UVB-mediated activation of NFκB (144). The cleavage of RelA/p65 subunit of NFκB was blocked by a pan caspase inhibitor N-benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone (Z-VAD-FMK) during EGCG-mediated apoptosis (140). EGCG can suppress NFκB activation as well as other pro-survival pathways such as PI3K/AKT/mTOR and MAPKs in human bronchial epithelial cells, which may contribute to its ability to suppress inflammation, proliferation and angiogenesis induced by cigarette smoke (145). Thus, NFκB is considered as a target for preventing cancer, and modulation of this pathway by EGCG could contribute to its chemopreventive potential.

#### 4.8.2. STAT

Signal transducer and activator of transcription (STAT) proteins are the signaling molecules that are activated by phosphorylation through janus kinase (JAK) or cytokine receptors, G-protein-coupled receptors, or growth factor receptors, or by intracellular non-receptor tyrosine kinase recruitment (146, 147). Seven mammalian STAT proteins have been identified. STAT3 and STAT5 have been implicated in multiple myeloma, lymphomas, leukemias, and several solid tumors making these proteins logical targets for cancer therapy. These STAT proteins contribute to cell survival and growth by preventing apoptosis through increased expression of anti-apoptotic proteins, such as Bcl-2 and Bcl-$X_L$. STAT3 has been shown to directly activate VEGF gene, which is responsible for increased angiogenesis. Elevated STAT3 activity has been detected in head and neck squamous cell carcinoma (148), leukemias (149), lymphomas (150) and multiple myeloma (151). EGCG has been shown to suppress STAT activation in tumor cells and down regulate the phosphorylation of STAT3 (124).

Consumption of green tea is able to mediate cardioprotection and enhance cardiac function during ischemia/reperfusion injury. Green tea extract (GTE) and EGCG inhibit STAT1 activation and protect the myocardium against ischaemia/reperfusion injury (152, 153). Because GTE-mediated cardioprotection is achieved, at least in part, through inhibition of STAT1 activity, a similar action can be implemented in the clinical setting to minimize STAT1 activation levels in patients with acute coronary artery disease.

#### 4.8.3. AP-1

Activator Protein 1 (AP-1) transcription factor is a protein dimer composed of members of the basic region leucine zipper protein superfamily, specifically, the Jun, Fos, and activating transcription factor proteins (154). AP-1 activity has been implicated in various cellular functions including proliferation, transformation, differentiation, and apoptosis (155, 156). High AP-1 activity has also been shown to be involved in the tumor promotion and progression of various types of cancers, such as lung, breast, and skin cancer (157, 158). AP-1 regulates many genes that contain the specific DNA sequences in the promoter region collectively called the TPA response element. One class of genes that AP-1 regulates is matrix metalloproteinases, which catalyze the proteolytic cleavage of extracellular matrix components; AP-1 activity has been associated with invasive and metastatic characteristics of cancer cells (159, 160). Recently, EGCG was shown to inhibit AP1 activity through the inhibition of MAPK, specifically, the JNK (161). EGCG increases involucrin gene expression, suggesting that it enhances normal human keratinocyte differentiation (162, 163). EGCG increases hINV (AP1 factor-regulated human involucrin) promoter activity that requires the presence of an intact hINV promoter AP1 factor binding site (163). Fra-1, Fra-2, FosB, JunB, JunD, c-Jun, and c-Fos levels are increased by EGCG treatment, as is AP1 factor binding to hINV promoter AP1 site. EGCG response requires Ras, MEKK1, MEK3, and p38 kinases. These studies demonstrate that in normal human keratinocytes, EGCG markedly increases, via a MAPK signaling mechanism, AP1 factor-associated responses. The mechanisms of action of other tea polyphenols are not well understood.

#### 4.8.4. Nrf2

Nuclear Factor-E2-related Factor 2 (Nrf2) is a key transcriptional factor that activates the antioxidant-reactive element (ARE) and in turn regulates the expression of antioxidant phase II detoxifying enzymes (164). It is interesting to note that the promoter region of heme oxygenase-1 gene (HO-1) contains the ARE sequence (165). The mode of transcriptional activation of Nrf2 is not fully understood. Even though, it was considered that several upstream signaling kinases, including protein kinase C (PKC), phosphoinositol 3-kinase (PI3K), and mitogen–activated protein kinases (p38, ERK1/2, and JNK) regulate Nrf2/ARE activity (164-166). However, it is still unclear which kinase acts as an upstream mediator of Nrf2. It was observed that human lung adenocarcinoma A549 cells, which belong to NSCLC, were significantly resistant to the induction of apoptosis by EGCG and these cells express high levels of constitutive HO-1 and Nrf2, as compared with other human cancer cells (167). Although Nrf2 plays a critical role in protection against pulmonary fibrosis, presumably through enhancement of cellular antioxidant capacity (168), HO-1/Nrf2 activation as a defense mechanism in carcinoma cells during lung carcinogenesis may lead to their resistance to chemopreventive and chemotherapeutic regimens.

## 5. Apoptosis and cell cycle

Apoptosis is the protective mechanism through which unwanted cells are eliminated from the system. This is essential for normal development, turnover and replacement of cells in the living system and serves as the protective mechanism against cancer. It was reported that EGCG induces cell cycle arrest and apoptosis in many cancer cells without affecting the normal cells (169, 170). EGCG induces the expression of Cdk inhibitor $p21^{/WAF1/CIP1}$, and $p27^{/KIP1}$, decreases the expression of cyclin D1 and inhibits Cdk2 and Cdk4 kinases (171-173). Thus, EGCG either exerts its growth-inhibitory effects through modulation of the activities of several key G1 regulatory proteins such as Cdk2 and Cdk4 or mediates the induction of p21 and p27. In regards to apoptosis, EGCG activates caspase-3 and caspase-9, regulates mitochondrial functions (release of cytochrome c and Smac/DIABLO, and depolarization of mitochondrial membranes), and cleaves PARP. These physiological events are critical for the mitochondrial-dependent apoptosis or cell-intrinsic pathway of apoptosis (174-177).

## 6. CLINICAL SIGNIFICANCE OF EGCG

### 6.1. Effects of EGCG on cancer

#### 6.1.1. Prostate cancer

Prostate cancer is the leading cause of cancer-related deaths among males in the U.S. Green tea and its major constituent EGCG inhibit the growth of a variety of human prostate cancer-cell lines. EGCG treatment of prostate cancer cells resulted in dose-dependent inhibition of cell growth, cell cycle arrest, and induction of apoptosis (171, 178-185). Chemoprevention involving the use of natural or synthetic agents to suppress, block or reverse the process of carcinogenesis could be an effective approach to reduce the incidence of prostate cancer. Indeed, prostate cancer represents an excellent candidate disease for chemoprevention, because it is typically diagnosed in elderly men. Consistent with this assumption, there is intense activity in defining chemopreventive agents and molecular targets for prostate cancer chemoprevention. Among the many such agents that are available, for a variety of reasons, naturally occurring nontoxic dietary substances are preferred. EGCG and related catechins were found to inhibit the growth of prostate cancer in cell culture, and xenografts and TRAMP models (12, 50, 171, 179-181, 184-187). A preclinical study has demonstrated the accumulation of tea polyphenols (PP) and theaflavins in the small and large intestine, liver, and prostate of C57BL/6 mice which received decaffeinated black tea diet (185). In a human clinical trail, tea PPs were greater in prostate samples from men consuming black (BT) and green tea (GT) than in men consuming a caffeine-matched soda control (SC) (185). Although tea PP were not detectable in serum, *ex vivo* LNCaP prostate cancer cell proliferation was less when cells were grown in media containing patient serum collected after BT and GT consumption relative to baseline serum. Thus, the tea polyphenols and theaflavins are bioavailable in the prostate where they may be active in the prevention of prostate cancer.

### 6.1.2. Lung Cancer

Green tea extracts at dose of 2% and EGCG at 1.2 mM in the drinking water inhibits lung tumorigenesis in mice treated with a potent nitrosoamine found in tobacco smoke (188). Oral administration of green tea and EGCG inhibits metastasis of Lewis lung carcinoma LL2 cells in mice (189). Since superoxide can enhance the invasiveness of tumor cells, EGCG radical scavenging activity may be related to its inhibition of cancer-cell invasion and metastasis (189). Green tea at a dose of 0.6% as the sole source of drinking water, reduces tumor multiplicity in transgenic mice treated with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) (190). Drinking tea for 4-8 weeks reduces NNK-induced expression of mouse lung oncogenes, such as c-*myc*, c-*raf* and c-H-*ras*, suggesting a possible mechanism of green tea action through modulation of oncogene expression (191).

### 6.1.3. Skin cancer

Skin is the largest body organ, and serves as a protective barrier against environmental insults such as UV radiation-induced damage. Much of the deleterious effect of solar UV radiation is caused by UVB (290-320 nm). UVB induces skin cells to produce reactive oxygen species (ROS), eicosanoids, proteinases, and cytokines; the inhibition of these mediators is considered to reduce skin damage. Antioxidants such as ascorbic acid and α-tocopherol have been demonstrated to produce photoprotective effects in some *in vitro* and *in vivo* studies (192). It was reported that EGCG treatment inhibits UVB-induced infiltration of leukocytes (macrophage/neutrophils), a potential source of generation of ROS and prostaglandin metabolites, which play critical roles in skin tumor promotion in multistage skin carcinogenesis (193, 194). Furthermore, topical treatment with EGCG prevented UV-induced suppression of the contact hypersensitivity in wild-type (WT) mice but had no effect in IL-12 knockout mice (195). Injection of anti-IL-12 monoclonal antibody to WT mice blocked the preventive effect of EGCG on UV-induced immunosuppression. These studies suggest that EGCG can prevent UV-induced immunosuppression, and this may contribute to the chemopreventive activity of EGCG in prevention of photocarcinogenesis.

### 6.1.4. Pancreatic cancer

Cancer of the pancreas is the fourth leading cause of cancer death in the United States. This year approximately 32,000 Americans will die from cancer of the pancreas. With an overall 5-year survival rate of 3% (196), pancreatic cancer has one of the poorest prognoses among all cancers (197). Aside from its silent nature and tendency for late discovery, pancreatic cancer also shows unusual resistance to chemotherapy and radiation. Only 20% of pancreatic cancer patients are eligible for surgical resection, which currently remains the only potentially curative therapy (198). The operations are very complex, and unless performed by surgeons specially trained and experienced in this procedure, they can be associated with very high rates of operative morbidity and mortality. Unfortunately, many cancers of the pancreas are not resectable at the time of diagnosis. There are limited treatment options available for this disease because chemo- and radio-therapies are largely ineffective, and metastatic disease frequently redevelops even after surgery. Therefore, there is an urgent need to discover novel and effective chemopreventive approaches for pancreatic cancer.

Despite these successes, there is clearly a great need to improve our understanding of the fundamental nature of cancer of the pancreas. Ductal cancer of the pancreas putatively evolves through multistage neoplastic transformation processes that are reflected in a series of histologically well-defined precursor lesions termed pancreatic intraepithelial neoplasias (PanIN) (199). On the molecular level, the interplay between different signaling pathways remains an area of active investigation. Mutations in the K-ras gene occur early, the inactivation of the $p16^{INK4A}$ gene at intermediate stages, and the inactivation of p53 and DPC/Smad4 at a relatively late stage (200, 201). On the tissue level, the cell type that gives rise to ductal adenocarcinoma is not well understood. Proposed cellular origins for pancreatic carcinoma include duct cells (199, 202), islet cells (203, 204), acinar cells (205-207), or rare undifferentiated precursor cells (208). Centroacinar cells have emerged as a candidate cell of origin based upon the persistent activation of the Notch pathway in these cells in adulthood (209). Although centroacinar cells constitute the terminal cells of the ductal system and contain ultrastructural features of ductal cells, the precise lineage of centroacinar cells has not yet been elucidated.

Pancreatic cancer becomes clinically apparent at late stages and it resists all forms of conventional chemotherapy and radiotherapy (196, 197). Therefore, understanding the pathogenesis of the preinvasive stage, and developing effective strategies to prevent pancreatic neoplasms are of paramount importance. It has been reported that the quantity of green tea consumed, plays an important role in reducing cancer risk and in delaying cancer outbreak and recurrence. EGCG can exert a growth-suppressive effect on human pancreatic cancer cells *in vitro* (13-15). It induces cell cycle arrest and apoptosis in pancreatic cancer cells and thus holds great promise for development as a chemopreventive agent. In addition, EGCG causes Bax oligomerization, generates reactive oxygen species (ROS), and depolarizes mitochondrial membranes to facilitate cytochrome *c* release into cytosol (14). Furthermore, EGCG activates c-Jun N-terminal kinase (JNK) in pancreatic carcinoma cells (14). Black and green tea extracts, GTP, and EGCG decreased the expression of the K-ras gene, and inhibited growth of pancreatic cancer cells (13). Thus, EGCG may be a potent biologic inhibitor of human pancreatic carcinomas, reducing their proliferative and invasive activities.

### 6.1.5. Breast cancer

EGCG was reported to be cytotoxic toward breast cancer cells. EGCG inhibited cell proliferation in MCF-7, BT474, Hs578t, MDA-MB-231, MBA-MB-468 and BT-20 cells, but had no effect on normal mammary epithelial cells (7, 38, 108, 175, 210-218). EGCG and

related polyphenols induced apoptosis in breast cancer cells through caspase activation and mitochondrial damage (7, 38, 108, 175, 210-218). EGCG inhibits the expression of cyclin D, cyclin E, CDK4, CDK1 and PCNA, which are correlated with cell cycle arrest at G1 (214). Studies in the ER negative cell line, MDA-MB-231, showed a very similar trend, with increased protein expression of $p21^{/WAF1/CIP1}$ and $p27^{/KIP1}$ following EGCG treatment (112). EGCG induced apoptosis in T-47D cells through caspase cascade and the cells were detained at the G1 phase. The rate of apoptosis and activity of caspase-3 induced by EGCG was time and dose dependent (215). Nude mice inoculated with human breast cancer MDA-MB-231 cells and treated with GTP and EGCG were effective in delaying the tumor incidence as well as reducing the tumor burden compared to control (214). GTP and EGCG treatment also induced tumor cell apoptosis and inhibited proliferation in xenografted nude mice. Thus, GTP and EGCG treatment inhibits proliferation and induce apoptosis of breast cancer cells *in vitro* and *in vivo*. All together, these studies strongly suggest that GTP and EGCG have anti-tumor properties.

**6.1.6. Ovarian cancer**

EGCG inhibited ovarian cancer cell growth, caused cell cycle arrest and induced apoptosis in SKOV-3 (p53 negative), OVCAR-3 (mutant type p53) and PA-1 (wild type p53) cells (219). The cell cycle was arrested at the G1 phase by EGCG in SKOV-3 and OVCAR-3 cells, whereas in PA-1 cells it exerted its effect at the G1/S phase. EGCG differentially regulated the expression of Bax, p21, Rb, cyclin D1, CDK4, Bcl-$X_L$, showing a possible gene regulatory role of EGCG. The continual expression in $p21^{/WAF1}$ suggests that EGCG acts in the same way with p53 proteins to facilitate apoptosis. Bax, PCNA, and Bcl-X are important in EGCG-mediated apoptosis. In contrast, CDK4 and Rb are not important in ovarian cancer cell growth inhibition. EGCG can inhibit ovarian cancer cell growth through induction of apoptosis and cell cycle arrest as well as regulation of cell cycle-related proteins. Thereby, the EGCG-mediated apoptosis can be applied to an advanced strategy in the development of a potential drug against ovarian cancer.

The endothelin (ET) A receptor (ET(A)R)/ET-1 autocrine pathway is overexpressed in ovarian carcinoma and triggers tumor growth, neoangiogenesis, and invasion. These latter tumor-promoting effects are mediated through the activation of cyclooxygenase (COX)-1- and COX-2-dependent pathways by ET-1. Pretreatment of HEY and OVCA 433 ovarian carcinoma cell lines with green tea and EGCG inhibited ET-1/ET(A)R expression, ET(A)R-mediated COX-1/2 mRNA expression, and COX-2 promoter activity (220). These effects were associated with a significant reduction in the COX-1/2-derived prostaglandin E2 (PGE2) production. These results provide a novel insight into the mechanism by which EGCG, by affecting ET(A)R-dependent COX-1/2 pathways may inhibit ovarian tumors suggesting that EGCG may be useful in preventing and treating ovarian carcinoma in which activation of ET(A)R by ET-1 plays a critical role in tumor growth and progression. The EGCG-induced inhibitory effects were also associated with a decrease in ET(A)R-dependent activation of the ERK1/2 and p38 MAPKs and PI-3K pathway (39).

Eight ovarian cancer cell lines were tested (SKOV3, CAOV3, OVCAR3, OVCAR10, A2780, CP70, C30, and C200) and showed IC50s for EGCG at the micromolar range, including ones that are resistant to the chemotherapeutic drug cisplatin (221). The ovarian cancer cells were sensitive to $H_2O_2$ at similar concentrations, and EGCG treatment led to enhanced intracellular $H_2O_2$ (221). Neutralization with pyruvate, a scavenger of $H_2O_2$, suggests that the toxicity of EGCG may be mediated by oxidative stress from the free radical. Addition of Tempol, a superoxide dismutase mimetic, demonstrates that $H_2O_2$ might be generated endogenously from superoxide. The toxicity of cisplatin and the development of cisplatin resistance are major obstacles in treatment of ovarian cancer. Interestingly, the addition of EGCG amplified the toxicity of cisplatin. EGCG significantly increased cisplatin potency in SKOV3, CAOV3, and C200 cells, the latter being a cell line induced to have several hundred fold resistant to cisplatin above the parental line. These findings suggest that EGCG may accentuate oxidative stress to inhibit growth of ovarian cancer cells and sensitize them to cisplatin.

**6.2. Effects of EGCG on angiogenesis and metastasis**

Angiogenesis, the formation of new capillaries from pre-existing vessels, is required for several physiologial processes as well as pathological conditions. It is composed of several steps which include the degradation of vascular basement membrane matrix by protease, migration and proliferaatin of endothelial cells into interstitium, endothelial tube formation, recruitment and attachment of mesenchymal cells to the endothelial cells tube, and maturation of blood vessels with the formation of vascular basement membrane (222). Upon angiogenic stimuli, proteases represented by matrix metalloprotease (MMP) are activated and, in turn, degrade vascular basement membranes, thus leading to the migration of activated endothelial cells into interstitium. Several proangiogenic (e.g. VEGF, bFGF, PIGF, G-CSF, HGF, angiopoietin-1/2, angiogenin, proliferin, PDGF-BB, TGF-α, TGF-β, TNF-α, IL-3, and IL-8) and antiangiogenic factors (e.g. IFN, PF4, angiostatin, endostatin, vasostatin, arrestin, angioarrestin, vasohibin, IL-4, IL-10, IL-12, IP-10, MIG) have been reported (222, 223).

VEGF is a mitogen for endothelial cells and is associated with tumor-induced angiogenesis. VEGF binds to VEGF receptors and is responsible for most of its mitogenic and chemotactic effects. EGCG inhibited microvessel density, endothelial cell growth, chemotaxis, invasion, VEGF receptor phosphorylation and induced apoptosis (224-226). EGCG inhibited phosphorylation of VEGF receptors and ERK1/2, and mRNA expression of the early growth response factor-1 (227). The inhibition of VEGF binding to its receptors may contribute to the antiangiogenic and cancer chemopreventive effects of EGCG. EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the

induction of VEGF. VEGF-induced IL-8 production at the mRNA and protein levels are also suppressed with EGCG (228). Furthermore, EGCG may exert the anti-angiogenic effect by inhibiting the PDGF-induced VEGF expression at multiple signaling levels (229).

Matrix metalloproteinases (MMP) that participate in extracellular matrix degradation are involved in the development of metastasis, epidermal detachment and hepatic fibrosis. MMP-2 and MMP-9, seems to play an important role in tumor invasion and metastasis. EGCG has been shown to affect MMP-2 and MMP-9 activity both directly and indirectly in endothelial cells therby inhibit or delay cancer invasion, metastasis, and angiogenesis via modulations in MMPs (46, 180, 230-235). MMP7 was shown to degrade *ex vivo* on healthy normal skin collagen VII and fibrillin 1. MMP7 could take an active part in the epidermal detachment occurring during recessive dystrophic epidermolysis bullosa (RDEB). EGCG inhibited MMP7 and developed a good protection of collagen type VII and fibrillin 1 susceptible of being degraded by MMP7 (231). Thus, EGCG could be used beneficially in patients suffering from RDEB. EGCG may also exert anti-fibrogenic activity (236). It inhibited expression of MMP-2 mRNA and protein in rat hepatic stellate cells (HSC) (236). EGCG treatment also reduced concanavalin A (ConA)-induced activation of secreted MMP-2 and reduced MT1-MMP activity. In addition, EGCG inhibited either HSC migration or invasion. The abilities of EGCG to suppress MMP-2 activation and HSC invasiveness suggest that EGCG may be useful in the treatment and prevention of hepatic fibrosis.

During tumor neovascularization, vascular endothelial growth factor and ephrin (Eph) families emerge as critical mediators of angiogenesis. EGCG inhibited ephrin-A1-mediated endothelial cell migration, as well as tumor angiogenesis (237). Furthermore, EGCG inhibited the ephrin-A1-mediated phosphorylation of EphA2 and ERK-1/2. Taken together, these data indicate that activation of ERK-1/2 plays an essential role in ephrin-A1-mediated cell migration, and suggest a novel anti-angiogenic role of EGCG in cancer chemoprevention.

The endothelin A receptor (ET(A)R)/endothelin-1 (ET-1) axis is overexpressed in ovarian carcinoma representing a novel therapeutic target. Treatment with green tea or EGCG inhibited ET(A)R and ET-1 expression and reduced the basal and ET-1-induced cell proliferation and invasion (39). The EGCG-induced inhibitory effects were associated with a decrease of ET(A)R-dependent activation of the ERK-1/2 and p38 MAPKs and PI3-K pathways. Remarkably, EGCG treatment resulted in a lowering of basal and ET-1-induced angiogenesis and invasiveness mediators, such as vascular endothelial growth factor and tumor proteinase activation. EGCG inhibited HEY ovarian carcinoma xenografts, and this effect was associated with a reduction in ET-1, ET(A)R, and vascular endothelial growth factor expression, microvessel density, and proliferation index. These results provide a novel insight into the mechanism by which EGCG, affecting multiple ET(A)R-dependent pathways, may inhibit ovarian carcinoma growth.

Catechin, conjugated with fatty acid (acyl-catechin), strongly inhibited DNA polymerase, HL-60 cancer cell growth, and angiogenesis (238). Catechin conjugated with stearic acid [(2R,3S)-3',4',5,7-tetrahydroxyflavan-3-yl octadecanoate; catechin-C18] was the strongest inhibitor in DNA polymerase $\alpha$ and $\beta$ and angiogenesis. Catechin-C18 also suppressed human endothelial cell (HUVEC) tube formation on the reconstituted basement membrane, suggesting that it may affect not only DNA polymerases but also signal transduction pathways in HUVECs. Based on these studies, it appears that acyl-catechins target both DNA polymerases and angiogenesis as anticancer agents. Furthermore, acylation of catechin may be an effective chemical modification to improve the anticancer activity of catechin.

## 7. CONCLUSIONS AND FUTURE DIRECTIONS

EGCG is a major constituent in green tea which is a popular beverage (next to water) and shown to afford protection against many cancer types. Green tea and its polyphenolic antioxidants are much more potent than vitamin C and vitamin E scavenging potentially carcinogenic free radicals. Dozens of studies have also demonstrated almost one-third of the cancers are caused by dietary and lifestyle-related habits hence, manipulation of the diet are being recognized as a potential strategy against 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. Stereoselective total synthesis of EGCG, and its structurally related catechins in the laboratory, could provide new sources of these compounds for investigational and biomedical use. Like most chemopreventive agents, EGCG also possesses limited systemic bioavailability. Furthermore, auto-oxidation of EGCG may be another problem of its reduced biological activity in humans. Recent studies have demonstrated the ability of EGCG to bind high affinity binding proteins as possible direct targets for the action.

Green tea polyphenols inhibit metastasis through regulation of urokinase and matrix metalloproteinases. Polyphenols reduced angiogenesis, in part by decreasing vascular endothelial growth factor production and receptor phosphorylation. Interestingly, EGCG reduced dihydrofolate reductase activity, which would affect nucleic acid and protein synthesis. Furthermore, it also acted as an aryl hydrocarbon receptor antagonist by directly binding the receptor's molecular chaperone, heat shock protein 90.

In conclusion, green and black tea polyphenols act at numerous points regulating cancer cell growth, survival, angiogenesis, and metastasis, and posses several other health benefits. These agents have shown promising results by their ability to inhibit carcinogenesis in laboratory studies. If these effects can be successfully translated into human studies then these agents may prove to be valuable adjuvant therapies in the future. Data from

clinical trails of tea polyphenols are needed to define the optimal dosing, schedule, toxicities, and clinical efficacy before widespread use can be recommended.

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**Send correspondence to:** Dr Rakesh K. Srivastava, Department of Biochemistry, The University of Texas Health Science Center at Tyler, 11937 US Highway 271, Tyler, Texas 75708-3154, Tel: 903-877-7559, Fax: 903-877-5320, E-mail: rakesh.srivastava@uthct.edu