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Review Article

Anticancer effects and molecular mechanisms of epigallocatechin-3-gallate

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ABSTRACT

Epigallocatechin-3-gallate (EGCG) is a type of catechin found in green tea. EGCG exhibits a variety of activities, including anti-inflammatory, antidiabetes, antiobesity, and antitumor. In this review, we focus on the antitumor effects of EGCG. EGCG inhibits carcinogen activity, tumorigenesis, proliferation, and angiogenesis, and induces cell death. These effects are associated with modulation of reactive oxygen species (ROS) production. Although EGCG has a dual function of antioxidant and pro-oxidant potential, EGCG-mediated modulation of ROS production is reported to be responsible for its anticancer effects. The EGCG-mediated inhibition of nuclear factor-κB signaling is also associated with inhibition of migration, angiogenesis, and cell viability. Activation of mitogen-activated protein kinases activity upregulates the anticancer effect of EGCG on migration, invasion, and apoptosis. In addition, EGCG could also induce epigenetic modification by inhibition of DNA methyltransferase activity and regulation of acetylation on histone, leading to an upregulation of apoptosis. Although EGCG promotes strong anticancer effects by multiple mechanisms, further studies are needed to define the use of EGCG in clinical treatment.

1. Introduction

Green tea is one of most consumed beverages around the world.[1] It is extracted from the leaves of *Camellia sinensis*, which is an evergreen shrub of the Theaceae family. Green tea is composed of proteins (15–20% dry weight), amino acids (1–4% dry weight), fiber (26% dry weight), carbohydrates (5–7% dry weight), minerals and trace elements (5% dry weight), lipids (5% dry weight), and polyphenols (30% dry weight).[2] Among polyphenols, green tea is characterized by the presence of large amounts of catechins, including epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate, and epicatechin (EC). Among them, EGCG has been known as the most powerful protective agent in cancer chemoprevention.[3] The beneficial effects of EGCG are reported in the treatment of cancer,[4] cardiovascular diseases,[5] diabetes,[6] neurodegenerative diseases,[7] and liver diseases.[8] This review describes the chemopreventive effect and molecular mechanisms of EGCG.

2. EGCG

2.1. *Structure of EGCG*

EGCG has three aromatic rings (A, B, and D) that are linked together by a pyran ring (C; Fig. 1). The health-promoting

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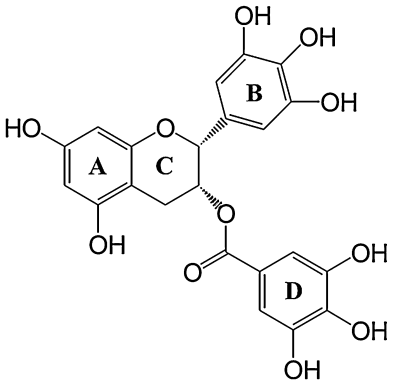

Fig. 1 – Structure of epigallocatechin-3-gallate. [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl]3,4,5-trihydroxy-benzoate. Molecular weight: 458.37.

function of EGCG is attributed to its structure. For example, the antioxidant activity of EGCG results from the transfer of hydrogen atom or single-electron transfer reactions, involving hydroxyl groups of the B and/or D rings.[9] Furthermore, the B and D rings are associated with an inhibition of proteasome activity *in vitro*.[10] The A ring of EGCG is involved in the inhibition of heat-shock protein 90.[11] The hydroxyl group at the 5′ position in the B ring also inhibits the growth of *Helicobacter pylori* in the stomach.[12]

2.2. *Bioavailability of EGCG*

A preclinical pharmacokinetic study reported that EGCG has low oral bioavailability (2–13%) in rodents.[13] Multiple processes contribute to the low bioavailability of EGCG, including the following: (1) low solubility in the gastrointestinal fluid; (2) slow and hard absorption; (3) fast metabolism and elimination system; (4) wide tissue distribution. A previous study by Yang et al[14] evaluated the bioavailability of tea catechins in humans. In that study, 18 individuals were given different amounts of green tea (1.5–4 g in 500 mL of water) and the time-dependent plasma concentrations and urinary excretion of tea catechins were evaluated. The maximum plasma concentration of EGCG was 326 ng/mL, which was detected at 1.4–2.4 hours after ingestion of the tea preparation; the half-life of EGCG was 5.0–5.5 hours.[14] Over 90% of EGC and EC were detected in urine within 8 hours,[14] and most EGCG was excreted in the bile.[15] Furthermore, EGCG is extracted by the presystemic hepatic system[16] and is eliminated by the intestinal efflux transporter.[17] In another study, rats and mice were given a 0.6% green tea polyphenol preparation for 14 days, and the distribution of EGCG was observed in multiple tissues. The highest concentration of EGCG was detected in the large intestine (1.1 μM); significant concentrations of EGCG were also found in the kidneys, prostate, and lungs.[18] Suganuma et al[19] suggested that frequent consumption of green tea aids in maintaining a high level of EGCG. Therefore, understanding the mechanisms of EGCG's biological effects could improve our understanding of its bioavailability as well as its role in chemoprevention.

3. Anticancer effects of EGCG

3.1. *Inhibition of carcinogen activity and tumorigenesis*

The initiation and progression of cancer are related to epigenetic alterations, including aberrant DNA methylation and acetylation. EGCG inhibits tumorigenesis of the lung, oral-digestive tract, and prostate. In A/J mice, EGCG inhibits the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis though inhibition of 8-hydroxydeoxyguanosine formation by antioxidant function.[20] In addition, EGCG inhibits cisplatin- or dimethylarsinic acid-induced lung tumorigenesis,[21,22] and diethylnitrosamine-induced liver tumorigenesis through the inhibition of insulin-like growth factor signaling in obese and diabetic C57BL/KsJ-db/db mice.[23] *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced carcinogenesis is also blocked by EGCG treatment in glandular stomach.[24] Oral administration of EGCG inhibits the growth of prostate cancer cells in xenograft models though the upregulation of apoptosis.[25] Although mechanisms of EGCG on anticarcinogenesis and antitumorigenesis are not clear, the anticancer effect of EGCG has been reported in multiple cancers.

3.2. *Inhibition of tumor proliferation and angiogenesis*

Tumor growth is closely related to angiogenesis, which provides oxygen and nutrients to tumor cells.[26] Vascular endothelial growth factor (VEGF) has been known as an important angiogenic factor. EGCG inhibits tumor growth and angiogenesis by the downregulation of VEGF expression in serum-deprived HT29 human colon cancer cells and *in vivo*.[27] In human pancreatic cancer and breast cancer cells, EGCG also reduces VEGF expression, resulting in inhibition of tumor growth and/or angiogenesis.[28,29] EGCG inhibits angiogenesis by the downregulation of VEGF and increases the cytotoxic T-lymphocyte infiltration into the tumor, thereby reducing the tumor in UV-induced skin tumors.[30] In human colorectal cancer cells, EGCG inhibits tumor growth and activation of VEGF receptor signaling.[31] In addition to inhibition of VEGF signaling, EGCG also modulates protein tyrosine kinase activity of epidermal growth factor receptor (EGFR) and Platelet-derived growth factor receptor (PDGFR), which is implicated as a contributing factor in the proliferation of cancer cells. EGCG modulates EGFR singaling through multiple ways: (1) inhibition of autophosphorylation of EGFR;[32] (2) increase of EGFR phosphorylation at Ser1046/1047 by p38 mitogen-activated protein kinase (MAPK) in colon carcinoma, resulting in the downregulation of EGFR expression;[33] (3) induction of EGFR internalization into the endosome;[34] (4) modulation of membrane lipid organization, and then inhibition of binding EGF to EGFR.[35] EGCG also inhibits PDGFR β-phosphorylation and downstream signaling in cultured vascular smooth muscle cells and spheroid formation of human glioblastoma cells.[36]

3.3. *Inhibition of tumor migration and invasion*

Inhibition of migration and invasion of tumor cells could be a target of anticancer therapy. EGCG downregulates hepatocyte

growth factor (HGF)-induced matrix metalloproteinase (MMP)-9 and activation of urokinase-type plasminogen activator (uPA) to inhibit invasion and metastasis in hypopharyngeal carcinoma cells.[37] Furthermore, inhibition of HGF-Met signaling by EGCG also blocks migration and invasion.[38,39] In melanoma cells and oral cavity cancer cells, EGCG decreases uPA activation and expression of MMP-2 and MMP-9 by suppression of HGF-Met signaling, respectively.[38,39] EGCG also modulates small guanosine triphosphatase proteins (Rac and Rho), which are important for cellular migration, and reduces activation of Rho A, and then inhibits invasion in the three-dimensional oral squamous cell carcinoma models.[40] Inhibition of Rac1 activity downregulates vasodilator-stimulated phosphoprotein expression, which results in blocking of cell migration and invasion in breast carcinoma cells.[41] In addition, EGCG inhibits migration of heregulin β1-induced breast carcinoma cells,[42] and invasion of thrombin-induced hepatocellular carcinoma cells.[43] EGCG inhibits medulloblastoma cell migration selectively on collagen through the upregulation of adhesion by induction of β1 integrin expression.[44]

3.4. *Induction of cell death*

3.4.1. *Caspase-dependent apoptosis*

Apoptosis has been known as a key strategy for the elimination of cancer cells. The ratio between antiapoptotic Bcl-2 families (Bcl-2 and Bcl-xL) and proapoptotic Bcl-2 families (Bax and Bak) decides the cellular susceptibility against anticancer drugs in cancer cells. Furthermore, BH3-only proteins (PUMA, Noxa, and Bim) bind with anti-Bcl-2 proteins to inhibit their functions, resulting in induction of apoptosis. Several studies have reported that EGCG modulates expression of the Bcl-2 family of proteins. EGCG induces apoptosis by the downregulation of Bcl-2 and/or upregulation of Bax expression in nasopharyngeal carcinoma cells,[45] breast carcinoma cells,[46] prostate carcinoma cells,[47] hepatoma cells,[48] bladder carcinoma cells,[49] and ovarian carcinoma cells.[50] Induction of PUMA by EGCG also leads to apoptosis in colon carcinoma cells.[51] Modulation of the expression of the Bcl-2 family of proteins by EGCG is one of the important factors for induction of apoptotic cell death. The p53 tumor suppressor gene plays a critical roles in the inhibition of tumorigenesis through cell cycle regulation, checkpoint activation, apoptosis, and DNA repair. Therefore, p53-mediated signaling is involved in apoptosis by anticancer drugs. EGCG could induce p53-mediated cell death through induction of stabilization and activity of p53. In both prostate and breast carcinoma cells, EGCG increases Bax expression, a downstream target of p53.[46,52] Furthermore, EGCG induces p53-mediated nonsteroidal anti-inflammatory drug-activated gene-1 expression, which has proapoptotic and antitumorigenic effects, in head and neck cancer cells.[53] EGCG regulates p53 expression, and most studies attributed this to the phosphorylation of p53 at the serine residue. Recently, acetylation of p53 by EGCG was also reported to increase p53 transcriptional activity by inhibition of class I histone deacetylases.[54] By contrast, Berindan-Neagoe et al,[55] reported that the knock down of p53 by small interfering RNA and EGCG have a synergic effect on the induction of apoptosis in cervical carcinoma cells. Berindan-Neagoe et al[55] suggested that a combination of the knockdown of p53 and EGCG leads to the activation of alternative apoptosis pathways. In addition, EGCG could modulate phosphatidylinositide 3-kinases/protein kinase B (PI3K/Akt) signaling, which is the activated signaling in most cancers. EGCG upregulates phosphatase and tensin homolog deleted on chromosome 10 expressions, which is a negative regulator of PI3K/Akt signaling, and then increases human pancreatic carcinoma apoptosis.[56] EGCG also induces apoptosis by the inhibition of PI3K/Akt pathway in bladder carcinoma cells.[49]

3.4.2. *Caspase-independent apoptosis*

Apoptosis is mainly modulated by caspases in both intrinsic and extrinsic pathways. However, apoptosis-induction factor (AIF) and endonuclease G (EndoG) are also involved in apoptosis in a caspase-independent manner. Both AIF and EndoG translocate to nucleus, cleave DNA, and then increase apoptosis.[57] Recently, Lee et al[58] reported that EGCG induces caspase-independent apoptosis in laryngeal epidermoid carcinoma cells. Although EGCG markedly decreases cell viability, caspase activation was not detected. Furthermore, caspase inhibitor also has no effect on EGCG-induced cell death. Lee et al[58] suggested that EGCG induces the reduction of the mitochondrial membrane potential, release of cytochrome c, and subsequent translocation of AIF and EndoG into the nucleus.

3.4.3. *Lysosomal membrane permeabilization-mediated cell death*

Lysosomes are cytoplasmic organelles, which have a lot of acid hydrolytic enzymes. Lysosome breaks macromolecules and nonfunctional organelles into small particles, and helps to reuse them as new materials. Lysosomal proteases are kept in lysosomes in normal conditions. However, lysosomal membrane damage leads to lysosomal membrane permeabilization (LMP),[59] resulting in the release of acidic contents and proteases. Excessive lysosomal membrane damage increases cell death, including apoptosis,[60] necrosis,[61] and LMP-mediated cell death.[62] Among them, LMP-mediated cell death is dependent on cathepsins rather than caspases.[59] Recently, Zhang et al[62] reported that EGCG induces nonapoptotic cell death through LMP in hepatoma cells. In a serum-free medium, EGCG increases reactive oxygen species (ROS) and cytosolic vacuolization due to lysosome dilation. Subsequently, cathepsins are released from the lysosome into the cytosol, and cathepsin inhibitors block EGCG-mediated cell death. Thus, it was suggested that EGCG could have anticancer effects by the new cell death mechanism (i.e., LMP).

3.4.4. *Autophagy*

Autophagy is essential for cellular homeostasis through the degradation of cellular constituents. During autophagy, cytosolic constituents are sequestered into double membrane vesicles (autophagosome), and then fuse with lysosome for degradation (autolysosome). Autophagy generally has a pro-survival effect on normal cells and cancer cells, but the deregulation or hyperactivation of autophagy activates cell death signals rather than survival signals. The formation of autophagosomes was measured with induction of LC3 II form and beclin-1, and the formation of autolysosomes was examined with the downregulation of p62. EGCG increases the LC3

II form and degrades p62 in mesothelioma cells.[63] When cells were treated with autophagy inhibitor (chloroquine), EGCG-induced apoptosis is increased.[63] Therefore, induction of autophagy by EGCG activates survival signal in mesothelioma cells. EGCG-mediated autophagy has protective functions in endotoxin-stimulated macrophage,[64] palmitate-treated vascular endothelial cells,[65] and UVB irradiation-treated retinal pigment epithelial cells.[66] However, understanding the effects of EGCG on autophagy requires further studies.

3.5. *Adjuvant*

The use of EGCG as an adjuvant could enhance anticancer effects of drugs through pharmacokinetics modulation. Multidrug resistance acts as a major barrier in drugs-mediated anticancer effects in cancer cells. A main mechanism underlying this multidrug resistance is overexpression of the P glycoprotein, which acts as an efflux pump of anticancer agents. The EGCG induces doxorubicin-induced multidrug-resistant carcinoma cell death and vinblastine-induced drug-resistant cell death through modulation of P-glycoprotein function.[67,68] EGCG also overcomes tamoxifen resistance in breast carcinoma cells by downregulating the activity of P glycoprotein as well as the activity of breast cancer-resistance protein.[69] By contrast, EGCG could directly bind with the anticancer drugs, resulting in the downregulation of anticancer effects. For example, EGCG binds with sunitinib, which is a multitargeted tyrosine kinase inhibitor.[70] In patients with metastatic renal cell carcinoma, EGCG interferes with the anticancer effect of sunitinib, and it is suggested that patients who are taking sunitinib should stop drinking green tea or at least have an interval of 4 hours between drinking green tea and taking sunitinib.[70] However, although high concentrations of EGCG (224 μM) antagonize the antitumor effect of bortezomib, low concentrations of EGCG (16 μM) had no antagonistic effect in prostate carcinoma xenograft models.[70] In other words, EGCG did not antagonize the anticancer effect of bortezomib, and therefore the antagonistic effect of EGCG might be dependent on species and concentrations.

4. Modulation of signaling molecules

4.1. *ROS: antioxidant versus pro-oxidant effects*

ROSs are critical signaling molecules that modulate anticancer effects. First, EGCG could directly scavenge ROS. The antioxidant activity of EGCG results from the transfer of hydrogen atom or single-electron transfer reactions, involving hydroxyl groups of the B and/or D rings. Electron paramagnetic resonance (EPR) spectroscopy and density functional theory calculations have been used to examine the redox properties of the green tea polyphenols, such as EGCG. Using EPR, it is reported that EGCG reacts with O^{2-}, which induces oxidation of the D ring.[71] Furthermore, EGCG also could efficiently scavenge OH and O^{2-}.[72] The antioxidant effect of EGCG is related to anticancer function. For example, EGCG reduces cell proliferation and induces apoptosis in low-dose H_2O_2 (10 μM)-treated colon carcinoma cells,[73] and downregulates 12-O-tetradecanoylphorbol-13-acetate-mediated oxidative stress in cervical carcinoma cells.[74] In addition, EGCG inhibits adhesion and invasion of hepatoma cells through its antioxidant properties.[75] EGCG could also indirectly downregulate ROS levels by induction of antioxidant enzymes. In EGCG-treated colon cancer xenograft models, EGCG markedly induced nuclear factor erythroid 2-related factor 2 (Nrf2) protein expressions, which is a critical transcription factor for the expression of antioxidant enzymes, resulting in the inhibition of tumor growth and metastasis.[76]

By contrast, a number of studies suggested the pro-oxidant effect of EGCG on anticancer function. EGCG under cell culture conditions is unstable and produces ROS by auto-oxidation.[77] EGCG-mediated ROS production is dependent on the concentration of EGCG, temperature, pH, and antioxidant levels in the culture condition. The half-life of EGCG is less than 30 minutes, and H_2O_2 formation was detected at 25 μM and 10 μM in McCoy's 5A culture media and in the presence of HT29 cells, respectively.[78] The production of ROS by auto-oxidation of EGCG is important for its cytotoxic effects in cancer cells. EGCG induces cell death by ROS production in pancreatic carcinoma cells,[79] in myeloid leukemia,[80] in human lymphoblastoid B cells,[81] in hepatocarcinoma cells,[82] in mesothelioma cells,[63,83,84] in endometrial adenocarcinoma cells,[85] and in laryngeal epidermoid carcinoma cells.[58] Moreover, *in vivo* studies also show that the pro-oxidant effect of EGCG is related to anticancer effects. Li et al[86] reported that oxidative stress by EGCG is involved in DNA damage-induced repair response and apoptosis.

4.2. *Nuclear factor-κB*

Nuclear factor-κB (NF-κB) has been known as a regulator of gene expression, which plays a critical role in the development and progression of various stages of cancer, such as proliferation, migration, invasion, and apoptosis. In normal cells, the dimer of NF-κB is sustained in cytosol due to its interaction with the inhibitors of NF-κB (IκB). When cells are stimulated by NF-κB activators, such as growth factor and proinflammatory cytokines, IκB kinase (IKK) phosphorylates IκB, following which IκB undergoes proteasome-dependent degradation. EGCG-induced prostate carcinoma apoptosis is associated with the downregulation of NF-κB activation, resulting in the downregulation of Bcl-2.[52] Downregulation of NF-κB activity by EGCG is also involved in cyclooxygenase-2 expression, which is an important enzyme for tumor cell proliferation, migration, and invasion.[87,88] In addition to apoptosis, inhibition of NF-κB by EGCG blocks invasion through reduction of MMP-9 expression in bladder carcinoma cells and lung carcinoma cells,[89,90] and inhibits proliferation and migration of colon carcinoma cells.[91] Moreover, EGCG inhibits VEGF production in head and neck carcinomas, suggesting the effect of antiangiogenic and antiproliferative activities.[92] A previous study reported that when transgenic prostate adenocarcinoma mice are supplemented with green tea polyphenols in their drinking water there was a reduction in the expression of NF-κB and IKK compared with control mice.[93] The mechanism of NF-κB inhibition by EGCG is suggested by suppression of IKK activation.[94]

4.3. MAPKs

MAPKs are composed of extracellular signal-regulated kinase (ERK), p38 MAPK, and c-Jun N-terminal kinase (JNK), and the deregulation of MAPK cascades contributes to cancer. Suppression of ERK phosphorylation by EGCG decreases MMP-2 and MMP-9 activity by the downregulation of MMP-2 and MMP-9 messenger RNA (mRNA) in fibrosarcoma cells,[95] and inhibition of ERK and JNK by EGCG reduces MMP-9 mRNA expression in phorbol 12-myristate 13-acetate-treated gastric carcinoma cells.[96] By contrast, EGCG promotes proMMP-7 production and mRNA expression by the activation of the JNK pathway in colorectal carcinoma cells.[97] In addition to migration and invasion, MAPK could regulate cell death. Activation of the JNK pathway is involved in EGCG-induced cytochrome c release and apoptosis in colorectal carcinoma cells,[97] and inhibition of ERK pathway downregulates cell growth and induces apoptosis in anaplastic thyroid carcinoma cells.[98] Regulation of MAPK signaling by EGCG could be markedly different in various cell types and depends on the concentration of EGCG.

4.4. Epigenetic modification

Cancer is modulated by both genetic and epigenetic events. Epigenetic events could alter gene expression without changing the primary DNA sequence, and epigenetic mechanisms include DNA methylation and histone acetylation. These epigenetic changes are involved in the alteration of gene function and expression, leading to malignant cellular formation. Among various epigenetic modifications, DNA methylation is most extensively studied in mammals. Hypermethylation on the DNA molecule limits the binding of transcription factors to promoters, resulting in the recruitment of additional silencing-associated proteins and gene silencing. This methylation is mediated by DNA methyltransferase (DNMT). EGCG has been known as an inhibitor of DNMT by direct inhibitory interaction with the catalytic site of DNMT.[99] EGCG reverses the methylation-mediated downregulation of the tumor suppressor $p16^{INK4a}$, retinoic acid receptor β, O6-methylguanine methyltransferase, and the DNA mismatch repair gene human mutL homolog 1 expression in esophageal cells, and then reduces cell growth and colony formation.[100] Furthermore, EGCG upregulates tissue factor pathway inhibitor-2 (TFPI-2), which is inversely related to an increasing degree of malignancy. EGCG reduces cell growth and increases apoptosis in renal carcinoma cells through the upregulation of TFPI-2 by EGCG-mediated demethylation.[101] In contrast to methylation, the upregulation of histone acetylation results in an open chromatin structure associated with transcriptional activation. In skin carcinoma cells, EGCG increases levels of acetylation on lysine of histone H3 and histone H4, leading to the upregulation of tumor-suppressor genes, $p16^{INK4a}$ and Cip1/p21.[102] However, EGCG also suppresses androgen-mediated transcription and cell growth by the downregulation of androgen receptor acetylation in prostate carcinoma cells.[103] Recently, Ko et al[104] reported that EGCG could negatively modulate Smad signaling by the inhibition of acetylation in lung carcinoma cells. The effect of EGCG on acetylation is controversial and is dependent on cell types and cell condition.

5. Safety of EGCG

Although tea polyphenols are safe and high consumption of tea polyphenols (600–1800 mg/day) has no adverse reaction, toxicity of EGCG has also been reported. Schmidt et al[105] reported that EGCG is a major contributor to the cytotoxic effect of green tea extracts in hepatocytes. Furthermore, treatment with EGCG enhanced high glucose-mediated beta-cell damage in diabetic rats.[106] EGCG increases the reduction of islet cell mass and number of insulin-positive beta cells through the production of ROS at nanomolar plasma concentrations.[106] In addition, there are many studies about the toxic effects of EGCG in inducing hepatic failure.[107–109]

6. Conclusion

EGCG promotes anticancer effects by modulation of multiple processes, including inhibition of carcinogen activity, tumorigenesis, proliferation, and angiogenesis, and induction of cell death. These effects are associated with modulation

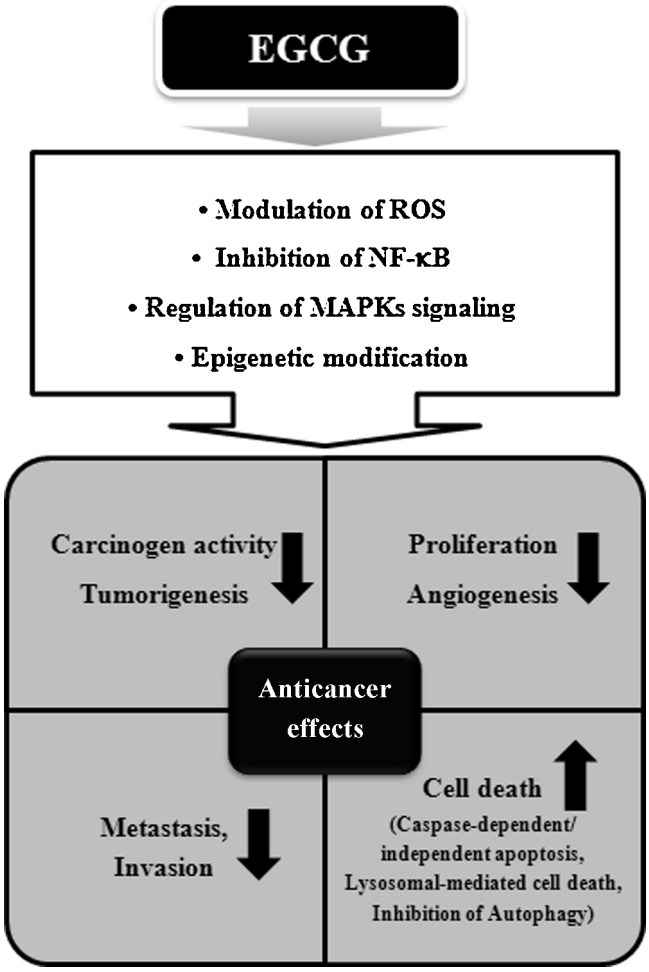

Fig. 2 – Anticancer effects and molecular mechanisms of EGCG.
EGCG, epigallocatechin-3-gallate; MAPKs, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; ROS, reactive oxygen species.

of ROS production, inhibition of NF-κB, down/upregulation of MAPKs activation, and regulation of epigenetic change (Fig. 2). Although EGCG exhibits a strong anticancer effect *in vitro*, further studies are needed to define the use of EGCG in clinical treatment.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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