

EGCG - A Promising Anti-Cancer Phytochemical.

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ABSTRACT

Constant research work and evidences over the years indicate that consumption of tea, especially green tea, is good for preventing cancer. A growing body of evidence suggests beneficial role of green tea and its polyphenol in oral cancer. To elucidate the cancer preventive mechanisms of green tea, much effort has been devoted to investigate the anticancer effects of Epigallocatechin-3-gallate (EGCG), the major catechin of green tea. It has been revealed that EGCG restrained carcinogenesis in a variety of tissues through inhibition of growth factor-related cell signaling, reducing inflammatory mediators such as COX-2 and thereby limiting bioactivity of PGE₂. It also enhances gene expression, modulates cellular proliferation and apoptosis. EGCG is a multi-potent anticancer agent, which not only provides solid evidence to support the anticancer potential of green tea, but also offers new ways for discovering multiple-targeted anticancer drugs.

Keywords: Cancer prevention mechanisms, Epigallocatechin gallate, Green tea.

INTRODUCTION

Over the last decade the focus of oncogenesis has shifted from the role of specific agents and hereditary factors to oxidative stress and inflammatory mediators. The use of antioxidants, phytochemicals and anti-inflammatory agents to prevent oncogenesis as well as using these agents as synergist along with available modalities of cancer therapies has been extensively studied.

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Drinking green tea, a suggestive health beverage is common for more than 2000 years. Green tea is derived from the young tender leaves of plant *Camelia Sinesis*. Green tea is a non-fermented form of tea, includes more antioxidant molecules and has more antioxidant potential than black tea [Figure 1].^[1] Approximately 30% of its dry weight is polyphenol, most of which are catechins.^[2] The green tea catechins mainly consist of (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechingallate (ECG) and (-)-epigallocatechin-3-gallate (EGCG), of which EGCG may be the most effective chemo-preventive agent and has

been extensively studied with different human cancer cell lines and several cancer animal models.^[3] It has been revealed that EGCG inhibited carcinogenesis in a variety of tissues including lung, bladder, skin, small intestine, prostate and breast.^[4-8] As to the molecular mechanisms, EGCG has the potential to inhibit the multiple targets implicated in the initiation, promotion and progression stage of cancers. Therefore, EGCG is regarded as a multiple-targeted anticancer agent with diverse activities.^[3] This paper highlights the effects of EGCG in tumor initiation, promotion and progression and provides an appraisal of EGCG utility in therapeutic management of cancer.

INHIBITION OF THE CANCER INITIATION STAGE BY EGCG

The molecular and cellular pathways to malignancy are complex which include damage to DNA and mutations in the genome. This results in changes in pathways directing apoptosis, leading to malignant transformations.^[1] It is well known that oncogene mutation and reactive oxygen species (ROS) play important roles in the cancer initiation stage. Oncogene mutation leads to procarcinogen activation by activating some phase I enzymes such as the cytochrome P450s. ROS actively participate in the metabolic activation of procarcinogens. EGCG can neutralize these procarcinogens by

inhibiting the activity of cytochrome P450 enzymes and modulating ROS.^[3]

Considerable evidence has demonstrated that EGCG is a powerful antioxidant. The ROS scavenging effects of EGCG were superior to those of ascorbic acid and α -tocopherol in many cases. EGCG has the ability to scavenge for free radicals due to possession of a phenolic hydroxyl group attached to the flavan-3-ol structure and thereby inhibiting lipid peroxidation.^[9] Besides, the pyrogallol structure of EGCG also confers the molecule with strong metal-chelating ability. As a result, EGCG can bind with transition metal ions and behave as a preventive antioxidant.^[10,11] Its high affinity towards the lipid bi-layers also facilitates the entry of EGCG into the nuclei of cancer cells.^[12]

| | NON-FERMENTED GREEN TEA | SEMI-FERMENTED OOLONG TEA | FERMENTED BLACK TEA |
|------------------------------|--|--|---|
| Manufacturing process | produced by briefly steaming the just harvested leaves, rendering them soft and pliable and preventing them from fermenting or changing color. After steaming the leaves are rolled, then spread out and "fired" (dried with hot air or purified in a wok) until they are crisp. The resulting greenish-yellow tea has a green, slightly astringent flavor close to the taste of the fresh leaf. | produced by partial fermentation of fresh leaves before drying | produced by post harvest fermentation before drying and steaming. |
| Major polyphenols | Epicatechin Epicatechin-3-gallate Epigallocatechin Epigallocatechin-3-gallate | | Theaflavin Thearubigin |
| Countries primarily consumed | China, Japan, India, North Africa, Middle East | South-eastern China, Taiwan | Western countries, some Asian countries |

Figure 1: Different forms of tea

INHIBITION OF THE CANCER PROMOTION STAGE BY EGCG

The cancer promotion stage is a reversible and a long-term process, in which some intracellular signaling pathways and proteins associated with cell cycle are involved. EGCG exerts its anticancer effect by interfering with many signaling pathways and modulating cell cycle [Figure 2].^[3]

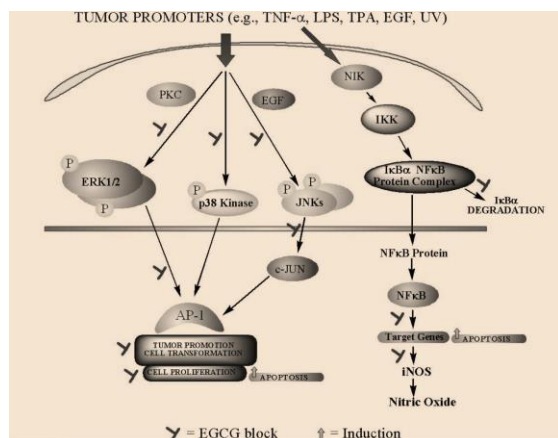


Figure 2: Intracellular signaling pathways and its modulation by EGCG.

It has been well accepted that NF- κ B signaling pathway plays a critical role in the control of cell growth and apoptosis.^[13] Based on the many

functions of NF- κ B target genes, a close relationship between NF- κ B and cancer has been proposed. Some studies have confirmed this hypothesis. Treatment with EGCG (10-40 μ mol/L) in a dose and time-dependent manner was found to inhibit UVB-mediated activation of NF κ B in normal human epidermal keratinocytes.^[14] Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are important enzymes that mediate inflammatory processes. Improper up-regulation of COX-2 and/or iNOS has been associated with pathophysiology of certain types of human cancers.^[3] It is found that EGCG could down-regulate the expression of constitutive COX-2, iNOS, mRNA and protein over expression thereby limiting bioactivity of PGE2. This in return leads to reduction in production of inflammatory mediators. It is also found that EGCG leads to decreased COX-2 promoter activity thereby causing decreased metastatic potential of cancer cells by altering the cellular membrane fluidity.^[1] EGCG also leads to rapid mRNA decay and post transcriptional control of gene expression. This helps in regulation of cell proliferation and apoptosis.

In addition, EGCG can also influence epidermal growth factor receptor-mediated signal transduction pathway. Over-expression of growth factor and growth factor receptors such as EGF receptor (EGFR), PDGF-Receptor (PDGFR) and others can result in a neoplastic phenotype in tumor cells.^[3] It has been reported that EGCG enhances growth inhibitory effects of 5-fluorouracil by inhibiting YCU-N861 and YCU-H891 gene expression. Studies suggest that EGCG inhibits activation of EGFR and the EGFR downstream signaling by inhibiting EGFR tyrosine kinase. These mechanisms lead to enhanced inhibition of cancer cell proliferation [Figure 3].^[1]



Figure 3: Anticancer effects of EGCG.

INHIBITION OF THE CANCER PROGRESSION STAGE BY EGCG

During the complicated processes of cancer progression, apoptosis and some enzymes such as urokinase and matrix metalloproteinases (MMPs) play a key role. Accumulating evidence indicates that EGCG can inhibit the growth of malignant cells by inducing apoptosis and inhibiting the

activity of some such enzymes. Apoptosis is an active form of cell suicide controlled by a network of genes, in which the Bcl-2 family of proteins plays important roles in control of apoptosis via regulating mitochondrial permeability and releasing of cytochrome c, which activates the caspase cascade. Apoptosis is an essential process which plays a critical role in the pathogenesis of diseases including cancer. EGCG has been shown to induce the apoptosis in a number of cancer cells. The inhibition was caused by the induction of apoptosis as a result of the activations of caspase-8, -9 and -3. These caspases appeared to be activated by the down regulation of Bcl-2 α and Bcl-xl.^[3] Furthermore, EGCG also acts on mitochondria and cytochrome C, increasing activity of apaf-1 and subsequently caspase-9.^[15] Several experiments show that EGCG enhanced the expression of GADD153 gene and induced apoptosis.^[1] EGCG also has a sealing effect as its mechanism of cancer prevention, that is, the treatment of cells with EGCG interrupts the interaction of cellular factors in membrane receptors by covering the cell surface and intracellular organelle [Figure 3].^[16]

CONCLUSION

Cancer is a dynamic process, in which a large number of genes and proteins are involved, to combat the initiation, promotion and progression of the disease. The potential of EGCG in hitting multiple targets implicated in various stages of cancer development not just provides solid evidence to support the anticancer effects of green tea, but also offers new evidence to justify the multiple-targeted antitumor activity. In addition, as the structure of EGCG holds the structural secrets of multi-potent anticancer agents, EGCG is expected to serve as a promising starting point to derive novel anticancer drugs.

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