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Journal of Cancer Prevention & Current Research

Review Article

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Epigallocatechin-3-Gallate (EGCG): mechanisms, perspectives and clinical applications in cervical cancer

Abstract

Cervical cancer represents the second leading cause of death for women worldwide. The importance of the diet and its impact on specific types of neoplasia has been highlighted, focusing again interest in the analysis of dietary polyphenols. Polyphenols have shown a wide range of cellular effects: can influence tumor suppressors and inhibit cellular proliferation, interfering in this way with the steps of carcinogenesis. From the studies concluded in this review, it is clear that certain dietary polyphenols especially epigallocatechin-3-gallate (EGCG) hold great potential in the prevention and therapy of cervical cancer, because they interfere in carcinogenesis (in the initiation, development and progression) by modulating the critical processes of cellular proliferation, differentiation, apoptosis, angiogenesis and metastasis, activating killer caspases, and suppressing oncogenic transcription factors and pluripotency maintain factors. . In vitro studies have demonstrated that EGCG blocks carcinogenesis by affecting a wide array of signal transduction pathways including JAK/STAT, MAPK, PI3K/AKT, Wnt and Notch.

An expanding body of preclinical evidence suggests EGCG, has the potential to impact a variety of human diseases. Much of the cancer chemopreventive properties of green tea are mediated by EGCG that induces apoptosis and promotes cell growth arrest by altering the expression of cell cycle regulatory proteins, activating killer caspases, and suppressing oncogenic transcription factors and pluripotency maintain factors. Various clinical studies have revealed that treatment by EGCG inhibits tumor incidence and multiplicity in different organ sites such as liver, stomach, skin, lung, mammary gland and colon. In this review, we discuss its cancer preventive properties and it's mechanism of action at numerous points regulating cancer cell growth, survival, angiogenesis and metastasis.

Keywords: cervical cancer, EGCG and apoptosis

Volume 9 Issue 4 - 2018

Sohail Hussain, Mohammad Ashafaq
Department of Biochemistry and Pharmacology, Jazan University, Kingdom of Saudi Arabia

Correspondence: Sohail Hussain, Department of Biochemistry and Pharmacology, Jazan University, Jazan, Kingdom of Saudi Arabia, Tel +966557632511, Email shussainamu@gmail.com

Received: November 13, 2017 | **Published:** July 12, 2018

Abbreviations: EGCG, Epigallocatechin-3-Gallate; GrTP, Green tea polyphenols; ROS, Reactive oxygen species

Introduction

Globally, cervical cancer affects approximately 490 000 women each year resulting in 270 000 mortalities.[1] In 2012 only in Europe there were 58,300 new diagnoses and nearly 24,400 deaths.[2] According to a study by the International Agency of Research for Cancer, it is expected that the mortality due to cancer may double in the next 50 years, rising to 15 million by the year 2020.[3] Several studies have proven that the cancer risk at the point of specific organs is due to exposure to specific environmental chemicals, biological agents (as Human Papilloma virus, Epstein Barr Virus, HIV1, HCV, Helicobacter pylori) or physical agents (such as ionizing radiation, UV).[4,5]

Several epidemiological studies from 2014 have reported the importance of the diet and its effects on specific types of neoplasia, raising again interest in the analysis of dietary phytochemicals.[6,7] It had been demonstrated that these compounds can interfere with cell regulation and proliferation, being involved in multiple signaling pathways that are disrupted during tumor initiation, proliferation and propagation. They can be found in vegetables, grains, fruits and other plant products.[8-11]

Daniele del Rio[12] reported in an extensive study from 2013 the importance of polyphenols in the prevention and treatment of various types of cancers, concluding that the anticancer effects of these natural compounds are still completely unknown, the studies with promising data indicated that regular consumption of green tea can interfere with the development of cancer.

Several studies on human and animal cervical cancer cells proved that polyphenols and their derivatives have antioxidant and anticancer potential. In the last years, the potential chemopreventive and chemotherapy properties of diet-derived agents have raised great interest among researchers. Recent studies have proposed the nanoformulation of polyphenols in order to prevent their rapid degradation and consequently enable delivery of increased concentrations to the target cells. The characteristics of an ideal chemopreventive agent are a selective approach to damaged cells, increased bioavailability in the lesion, multiple mechanisms of action and easy administration. Because of these specificities, dietary compounds are considered the best chemopreventive agents.[13,14] Among these dietary compounds, polyphenols have shown benefit activity as they have anti-proliferative and cytotoxic effects toward cancerous cells.[15,16]

Epigallocatechin-3-gallate (EGCG): Green tea, which contains powerful antioxidants, is one of the most popular beverages

consumed around the world. Of all the antioxidant compounds found in green tea, the major constituents are polyphenols, including phenolic acids and catechins. Catechins from green tea belong to the family of flavonoids that are powerful antioxidants and free iron scavengers. Many botanical flavonoids possess strong antioxidant activities in the cardiovascular system.[16] Effects of green tea on cancer chemoprevention have been attributed to its antioxidant activities.[17,18]

The purified green tea polyphenols (GrTP) contain >95% polyphenols when analyzed with high-performance liquid chromatography (HPLC). Pure GrTP extracts contain the following percentage composition of polyphenols (each catechin): (−)-epicatechin (EC) 35%, (−)-epigallocatechin (EGC) 15%, (−)-epicatechin-gallate (ECG) 4%, and (−)-epigallocatechin-3-gallate (EGCG) 38–40%. Among these components, EGCG is the most abundant tea polyphenol. The molecular structure of EGCG, are presented in the Figure 1.

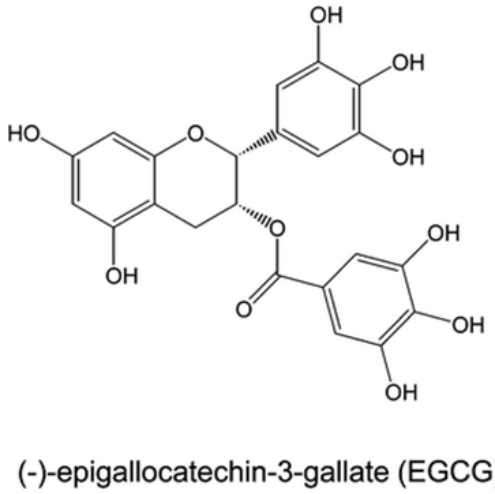


Figure 1 Molecular structure of (-)-epigallocatechin-3-gallate (EGCG).

Polyphenols share various therapeutic effects against pathological conditions including cancer, inflammation, diabetes, and cardiovascular diseases.[20,22] Recently, scientific interest in polyphenols has been rapidly increased. Moreover, it is reported that the galloyl moiety of tea catechins plays crucial roles in benefits of tea catechins, especially in lipid lowering effect.[23,24] Compared to other tea catechins, galloyl moiety of catechins (EGCG and ECG) possesses the most biological activities including angiogenesis.[25] Peoples believe that drinking green tea is beneficial to health and it has been demonstrated that EGCG is having inhibitory effects in many aspects of abnormal changes, such as antioxidant, anticancer, anti-inflammatory, anticollagenase, and antifibrosis effects, appearing in its wide functional range.[26,27] It can be speculated that EGCG, to some extent, has the effect of protecting organs or tissues from a pile of diseases. Moreover, EGCG has promotional effect on osteogenesis.[28-30] Although the researches concerning EGCG are still facing few controversies, EGCG is more likely to be beneficial to health.

Properties of EGCG

Antioxidant effect: An antioxidation system is a process of vital importance to the health of human body. On the basis of the chemical structure of EGCG, we sort it into antioxidant. The phenol rings in EGCG structure act as electron traps and scavengers of free radicals[31,32] reduce the formation of reactive oxygen species, and reduce the harms from oxidative stress.[33] It is reported that EGCG can effectively inhibit oxidative stress-induced protein tyrosine nitration induced by oxidative stress in blood platelet,[34] and improve the function of mitochondria.[35] However, it is also reported that high concentration of EGCG can cause self-oxidization and function as the prooxidant[36-39] by producing hydroxyl radicals, hydrogen peroxide, and quinonoid intermediates causing cytotoxicity.[40] For example, erythrocytes membrane protein aggregation due to catechol-quinone produced by self-oxidation of EGCG and EGC.[41] Meanwhile in factual physiological concentration (1-2 μM up to 10 μM), EGCG can produce small quantities of reactive oxygen species to activate several signal pathways and then arouse corresponding cellular protective mechanism, thus mainly presenting its antioxidant effects.[42,43] The complicated biological effects of EGCG may be linked to its products of the metabolism.[44]

Anticancer effect: The anticancer property of EGCG is the focus point of researches. On one hand, EGCG can inhibit tumorigenesis by inhibiting carcinogen activity.[42,45] On the other hand, it can restrain tumor proliferation by acting against angiogenesis.[46-49] Brahma et al.,[50] found that EGCG inhibits cervical cancer orthotopic tumor growth, angiogenesis, and metastasis that are associated with inhibition of PI3K/AKT and ERK pathways and activation of FKHRL1/FOXO3a.[50] Moreover, it can inhibit tumor migration and penetration[51-54] and induce tumor cell death via several mechanisms including caspase-dependent apoptosis, caspase-independent apoptosis, lysosomal membrane permeabilization-mediated cell death, and autophagy.[27,55] It is widely accepted that tumor migration and invasion is inhibit by EGCG has the capacity to suppress its activity.[56] In fact, most of the anticancer effects of EGCG play a role via several signal transduction pathways including JAK/STAT, MAPK, PI3K/AKT, Wnt, and Notch.[49,51,57-59] Recently, EGCG inhibited lipopolysaccharide induced nitric oxide production and inducible nitric oxide synthase gene expression in isolated peritoneal macrophages by decreasing the activation of NF-κB.[60] Moreover, they suppress the NF-κB and the activating protein (AP-1), inhibit the mitogen-activated proteins (MAPKs), the protein kinase and growth factor receptor-mediated pathways, are involved in cell cycle arrest and possess anti-inflammatory properties.[18,47,60,61] From the above mentioned points, it is more obvious that the mechanism of anticancer effect of EGCG is considerably multiple and complicated.

Moreover, the study conducted by Qiao et al.,[62] mentions several other aspects of the use of EGCG: inhibition of HPV E6/E7 expression, ER and aromatase. Other researchers, Sharma et al.,[63] studied HeLa cells treated with EGCG and reported a time-dependent manner of growth inhibition mediated through apoptosis. Along with the EGCG, polyphenol E also derived from green tea had inhibitory effects on cervical cancer.

After the promising results of in vitro studies, several clinical studies regarding the anticarcinogenic effects of polyphenols on cervical cancer were conducted. EGCG and curcumin were the most investigated compounds. The second most investigated polyphenolic compound in the treatment of cervical cancer lesions was EGCG. The investigation on the clinical efficacy of EGCG and also other green tea compounds (poly E capsule 200 mg EGCG, 37 mg epigallocatechin, and 31 mg epicatechin) in patients with HPV cervical lesions. Their results pointed out that 60% of patients under EGCG capsule therapy, 50% under poly E capsule therapy, 74% under poly E ointment therapy and 75% under poly E ointment plus poly E capsule therapy showed a response, mainly a 69% response rate as compared with a

Citation: Hussain S, Ashafaq M. Epigallocatechin-3-Gallate (EGCG): mechanisms, perspectives and clinical applications in cervical cancer. *J Cancer Prev Curr Res.* 2018;9(4):178–182. DOI: 10.15406/jcpcr.2018.09.00345

10% response rate in untreated controls. They concluded that green tea compounds used orally±vaginally are effective in the treatment of HPV-related cervical lesions.[64]

EGCG and its possible side effects

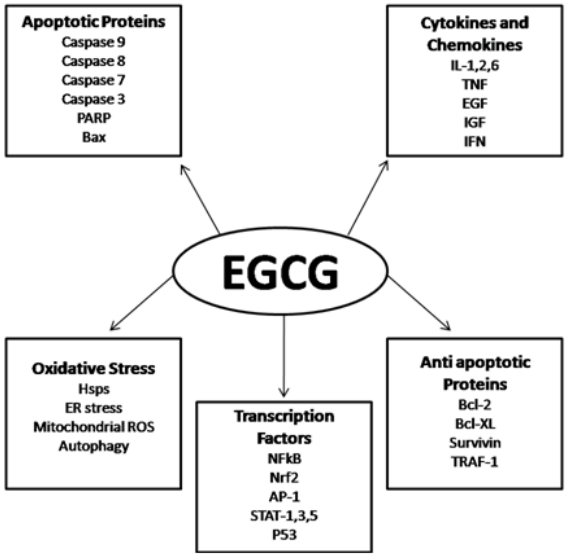
Tea, a popular beverage, has been consumed for many centuries. A preclinical trial described EGCG to have no detectable side effects at 800 mg/day in subjects.[65] However, some deleterious effects of tea and its components are as follows: tea is a known diuretic agent; overuse may result in dehydration. Prolonged supplementation may alter bile acid synthesis and increase hepatic oxidative stress with inflammatory hepatic injury, as reported in mice fed high cholesterol diets.[66] Weight loss may be considered a beneficial as well as a side effect of high dose GrTP (2.6 mg/g)[67] and EGCG consumption (1.3 mg/g)[67] 3.2 mg/g.[68] Although tea has antimicrobial and antifungal properties, different toxic metals[69] and microbial contaminations such as Clostridial spp. have been isolated from unpasteurized tea.[69] Clostridium difficile (C. diff) is a facultative gram negative microbial which can cause recurrent and life threatening complications in about 0.2% of the population.[70] It was suggested that tea in the gut of these patients may reduce the normal microbiome and provoke overgrowth of the facultative pathogens.[71]

Therefore, EGCG is counter-regulated by the presence of iron and lipocalin 2. EGCG prevents the peroxidase-catalyzed reaction by reverting the reactive peroxidase heme (compound I: oxoiron) back to its native inactive ferric state, possibly via the exchange of electrons.[72] Therefore, dietary oral intake of iron tablets can diminish EGCG, rendering it to become ineffective in inhibiting myeloperoxidase activity as an antioxidant to establish mucosal protection and anti-inflammatory effects of EGCG.

Mechanism of cervical cancer

Cervical cancer progress is recognized as a complex and multistep process in which discrete mechanism of molecular and cellular modifications occur. The progression defined in three stages: (1) initiation is defined as exposure or uptake of carcinogenic agent that especially interact with cell DNA leading to genotoxic damage, (2) promotion is considered as irreversible process in which abnormal proliferating cell may originate a focus of preneoplastic cells, (3) progression is a uncontrolled transformation and growth of the tumor cell, which involves the gradual conversion of premalignant cells to neoplastic ones.

Inhibition of oxidative damage constitutes the first line of defense system against cervical cancer by scavenging the reactive oxygen species. EGCG exhibit potent antioxidant and anticancer agent exerts its effect by modulating one or more signaling pathways that interrupts the carcinogenic process.



Mechanism of action of EGCG

Discussion and conclusion

EGCG shows various effects in different cell types in vitro and vivo. Notwithstanding the fact that the properties of the EGCG have been gradually clarified, there still exist quite a few controversies, for example, mechanism of EGCG in collagen stabilization. For the aspect of application, EGCG combined with other drugs for anticancer treatment can possess a synergistic and protective effect. Moreover, EGCG collagen membranes have great potentials in GBR surgeries. However, EGCG still encounters lots of challenges for clinical application. Oral administration or venous injection of EGCG has low bioavailability, and effects are easily influenced by concentration, derivatives, and other factors. It still needs solutions as to how to deliver EGCG effectively to target sites and protect anticancer drugs from degradation.

Acknowledgements

Authors want to thanks lab colleagues for reviewing the articles grammatically.

Conflict of interest

No conflict of interest between the authors.

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