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Review Article

Green Tea Polyphenol, Epigallocatechin-3-Gallate (EGCG): Mechanisms and Application on Hepatocellular Carcinoma

Ke-Wang Luo[1,3#], Wai-Fong Fung[1,2#], Wing-Yin Lung[1], Xin-Le Luo[3] and Wei-Ren Huang[1*]

[1]*Key Laboratory of Medical Programming Technology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, China*
[2]*Division of Biochemistry, School of Biomedical Science, the University of Hong Kong, Pokfulam, Hong Kong*
[3]*Key Laboratory, Shenzhen Longhua District People's Hospital, Shenzhen, China*
[#]*both authors contributed equally*

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***Corresponding author**

Wei-Ren Huang, Rm 205, Surgical Building, no. 3002, Sungang west road, Shenzhen Second People's Hospital, Shenzhen 518000, China, Tel: 86-136 0304 6629; Email: pony8980@163.com

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Abstract

Green tea is one of the most popular beverage consumed worldwide especially in Asian countries, and the most abundant and bioactive polyphenol in green tea is Epigallocatechin-3-gallate (EGCG). EGCG was demonstrated to have various biological activities, including anti-oxidation, anti-obesity, anti-cancer etc. This review focuses on the recent advances of EGCG and its applications in prevention and treatment of liver cancer. The mechanisms of actions of EGCG on liver cancer include induction of apoptosis and cell cycle arrest, inhibition of tumor metastasis and angiogenesis, and these actions would result in inhibition of cancer development. Besides, we discussed the previous and current ongoing clinical trials and scientific research studies of EGCG on liver cancer. This review holds the promise for the further application of EGCG as a potential anticancer supplement against liver cancer either used alone or in combination with other therapeutics.

Introduction

Green tea is one of the well-known beverages worldwide, especially in China and Asian countries, which is obtained from the dried leaves of the plant Camellia sinensis [1]. Green tea contains as many as 200 bioactive compounds, including tea polyphenols (catechins and flavanols), caffeine, theanine, vitamins and minerals. The most abundant group of tea components is tea polyphenols, including epicatechin (EC), epigallocaetchin (EGC), epicatechin-3-gallate (ECG) and epigallocatechin-3-gallate (EGCG) [2]. Green tea extracts and polyphenols used for biomedical purposes is increasing for treatment of various diseases such as cancer, obesity, cardiovascular diseases, diabetes mellitus, and so on [3-4]. Given the increasing popularity and commercial development of green tea and EGCG supplements in cancer treatment, in this review, we focused on the therapeutic implications and the mechanism of EGCG on liver cancer.

Tea Polyphenol EGCG

Green tea is very rich in tea polyphenol, especially flavanols and flavonols, which occupy approximately 30% dry weight of the fresh leaf [5]. Catechins are the predominant flavanols in green tea, characterized by having benzopyrane skeleton, with the pyrene ring bearing at least one aromatic ring [6]. There are four kinds of catechins in green tea, including EC, EGC, ECG, EGCG, and EGCG was found to be the most abundant and potent ingredient in green tea, which accounts for about 4-6%weight of dried tea, and 50-80% representing 200-300 mg in brewed cup of green tea [7].

The stability of EGCG is varied from acidic to alkaline condition. EGCG is less stable in neutral and alkaline medium, because basic medium will trace and attack the hydroxyl groups of phenyl ring of EGCG and resulted in the oxidation of EGCG [4]. The auto-oxidation of EGCG could be prevented by addition of superoxide dismutase in the medium [8]. Recently, some reports demonstrated that formation of nano particles of EGCG helps to improve its in vitro and in vivo effect [9-10].

EGCG was demonstrated to have a variety of biomedical effects, such as anti-oxidation, anti-cancer, anti-obesity, etc [4]. Epidemiological studies have shown that intake of green tea polyphenol EGCG resulted in a lower risk of several cancer types, including liver, stomach, prostate and lung cancers [11]. EGCG was shown to be effective in inducing apoptosis in a variety of cancer cells including leukemia, breast, lung and liver cancer cells [12-13]. In the following part, we discussed the mechanisms and therapeutic implications of EGCG in liver cancer.

Mechanisms of Action of EGCG on Cancer

EGCG has been proved to be effective in inhibition of various cancer types. The inhibitory effects of EGCG on cancer have been demonstrated both in vitro and in vivo, and the underlining anti-cancer mechanism including apoptosis induction and cell cycle arrest, inhibition of metastasis and angiogenesis, and affecting signaling pathways [2-4].

Induction of apoptosis and cell cycle arrest

Apoptosis, a type of programmed cell death, plays an important role in the normal development and differentiation of multicellular organisms [14]. It is responsible for scavenging the unwanted cells and is crucial for replacement of old cells and turnover. Generally, apoptosis is induced through two main pathways: the extrinsic pathway (death receptor pathway) and intrinsic pathway (mitochondria pathway). In the extrinsic pathway, the combination of stimulator and death receptor will result in the activation of caspase-8, which in return propagate the apoptosis signal and destroy the nucleic acid of cells [15]. While in the latter case, changes in mitochondria integrity and cytochrome C released are important steps, and the caspase-9 is usually activated through the formation of apoptosome [16].

Induction of apoptosis is one of the important strategies for the treatment of tumors. It is reported that EGCG could induce apoptosis in a variety of cancer cells without affecting normal cells [17-18]. Wang et al. demonstrated that EGCG up-regulated the expression of Fas and Bax, down-regulated Bcl-2 expression, then activated caspase-8, 9 and induced apoptosis in Jeko-1 cells and Raji cells through death receptor pathway and mitochondrial pathway [10]. Zhang's study showed that breast cancer patients oral administrated of EGCG capsules after radiotherapy, resulted in the decrease of Bcl-2/Bax and the activation of MMP-9 and MMP-2, then triggered a chain reaction by capsizes family, and at last induced apoptosis in breast cancer cells and prevent cancer cell migration [19]. EGCG induced apoptosis mainly occurs in cancer cells, and no obvious cytotoxicity or side effects shows on normal tissues and cells. In addition, EGCG can affect the expression of cell cycle proteins and result in the cell cycle arrest [20]. It has been shown that EGCG induced cell cycle arrest and apoptosis in several cancer cell lines including lung, liver, colon, prostate and skin cancer with minimal effect toward normal cells [21]. EGCG induced cell cycle arrest at G2/M phase in both CaSki and HeLa cell lines. Qiao et al. demonstrated that treatment with EGCG for 24 h resulted in a significant G2/M arrest and sub-G1 population production. EGCG was found to be effective in increasing sub-G1 ratio in HeLa cells [22]. Besides, it was demonstrated that EGCG significantly increased the cell percentage in sub-G1 phase. Luo et al found that hepatocellular carcinoma HepG2 cells treated with EGCG at 100 μM resulted in the increasing of G1 phase cells from 33.8% to 57.2%, and the decreasing of G2 phase cells from 34.3 to 11.9%, there by resulting in cell cycle arrest [23].

Inhibiton of metastasis

Metastasis refers to the process of cancer cells transfer from the primary site to distant locations by invasion of blood or lymph vessels. Metastasis usually occurs in 5 stages. Firstly, cancer cells break down the basement membrane, secret matrix metalloproteinases (MMPs) and detach from the primary tumor, and then the cancer cells penetrate into the blood or lymph vessels and circulate in the channel system, after breaking away from the vessels, the cancer cells invade into other tissue locations of the body and at last develop a secondary tumor [24]. Metastasis is an important and key challenge for cancer treatment. Varieties researches revealed that EGCG prevented cancer metastasis both in vitro and in vivo through inhibition of MMPs or the urokinase activity in the cancer cell lines, such as human melanoma, hepatocellular carcinoma cells and breast cancer cells [25-27]. A research from Yamamoto et al. revealed that EGCG showed strong anti-metastasis effect on the HT1080 cells and regulated MMP-2 and MMP-9 expression to digest gelatin. They found that EGCG was able to interact with metal ions or proteins and forming complexes. Hence, the inhibition effect of EGCG towards enzymatic activity of MMP-2 and MMP-9 depends on its property to chelate zinc metal ion, and then affect the enzyme activities and inhibitory effect of cancer cell metastasis [25]. EGCG also showed anti-metastasis effect on Hepatocellular carcinoma. Zhang et al showed that EGCG inhibited the metastasis in HCCLM6 cells with the suppression of MMP-2 and MMP-9 activity [26]. Besides, Slivova et al. used green tea polyphenols which containing 50% EGCG to test the anti-invasive ability towards breast cancer MDA-MB-231 cells. They found out that green tea polyphenols decreased the activity of transcription factors activator protein 1 (AP-1) and NF-KB, and hence led to further inhibition of the release of uPA and finally inhibited tumor metastasis [27]. In addition, EGCG also showed the inhibitory effect of metastasis in lung cancer, gastric cancer [28-29]. These results suggested that EGCG exerts its anti-metastasis effect in several cancers by decreasing the expression of MMPs and uPA.

Inhibition of angiogenesis

Angiogenesis is a multiple process that involves in the formation of new vascular network from the pre-existing blood vessels, which is involved in normal physiological processes, and also plays a crucial role in tumor development, invasion and metastasis [30]. Angiogenesis involves in many complex events like basement membrane degradation, endothelial proliferation and migration, and vascular tube formation. During the process of angiogenesis, vascular endothelial growth factor (VEGF) plays a key role, which is a mitogen for vascular endothelial cells and stimulates the proliferation. Over expression of VEGF can be seen in cancers and enables tumor to grow fast and metastasizes [31].

EGCG has been proofed to inhibit the growth of angiogenesis in animals by inhibiting of VEGF, blocking epidermal growth factor receptor (EGFR) signaling, suppressing Erk-1 and Erk-2 activation [10]. There are reports showed that EGCG was effective in cancer treatment by inhibiting angiogenesis in lung cancer, colon cancer and hepatocellular carcinoma cells [32-35]. Sakamoto et al revealed that the occurrence of angiogenesis is depend on the balance of pro-angiogenic factor VEGF and the anti-angiogenic factor endostain, which can inhibit the proliferation of endothelial proliferation. EGCG was able to increase the mRNA expression of endostain and decrease the mRNA expression of VEGF in a time-dependent manner. Hence, decreasing the VEGF production and increasing the endostain expression in A549 cells would make a balance to inhibit the angiogenesis of these cancer cells [32]. Jung et al showed that EGCG inhibited the growth of serum-deprived HT29 human colon cancer cells by inhibiting the induction of VEGF. They found out EGCG can block the Erk-1 and Erk-2 pathway, which is believed to be

the crucial signaling cascade for the induction of VEGF mRNA over expression [33]. In addition, Zhang et al revealed that green tea extract and EGCG inhibited serum-induced HIF-1α and VEGF expression by interfering with the PI3K/Akt signaling pathway in hepatocellular carcinoma HepG2 cells [34]. Bruns et al reported that EGFR is the up-stream regulator for the VEGF. After the EGFR signaling pathway activated by epidermal growth factor (EGF), the down-stream factors would be phosphorylated and caused the over expression of AP-1, which would bind to and activated VEGF [35]. Thus, targeting the EGFR signaling pathway by EGCG would be effective in inhibition of angiogenesis, and for prevention and treatment of cancer. Sur et al found that EGCG restrict of liver carcinogenesis in hepatocyte progenitor cell/stem cell by modulation of Wnt/Hh regulatory pathways and decrease the expression of CyclinD1, cMyc and EGFR [36].

EGCG affects signaling pathways

EGCG has been demonstrated to be effective in cancer prevention both in vitro and in vivo [2-4]. Kanwar et al demonstrated that EGCG induced apoptosis through MAPK, NF-κB, PI3K/Akt, CDK pathways [10]. Mitogen activated protein kinase (MAPK) are a group of serine/threonine kinases that act as signal transducers of cell proliferation. EGCG has been demonstrated to be effective in regulating molecules in the MAPK pathway thereby inhibiting cancer cell survival. EGCG significantly inhibited extracellular regulated kinase (ERK), interfered with MAPK signaling and then inhibited cancer cell proliferation [37]. Chang et al found that EGCG could inhibit the phosphorylation of ERK1/2, down-regulate the expression of MMP-2, and then inhibited metastasis of melanoma M17 cells [38]. Nuclear transcription factor NF-kappa B is a stress transcription factor, involved in a variety of important physiological process, including inflammation, immunity and apoptosis. EGCG could inhibit NF-κB signaling cascade and then suppress tumor growth. Li et al found that EGCG inhibited the transcription of NF-κB p65 and interfered with its intracellular localization, then suppressed the activation of NF-κB p65, thereby inhibited proliferation and metastasis of nasopharyngeal cancer stem cells [39]. EGCG was also demonstrated to be effective in inhibiting the activities of NF-κB in human cervical and gastric cancer cells [40-41]. Fang et al elucidated that EGCG inhibited NF-κB activation through down-regulation of ERK and MMP-9, thus suppressed cancer cell proliferation and metastasis [42]. PI3K/AKT, a pro-survial pathway, is closely related to cell growth, apoptosis, vascular formation and intracellular lipid metabolism processes. Muthusami et al., found that EGCG can down-regulate the expression of fusion protein FTS, inhibited the phosphorylation of AKT and induced apoptosis of cervical cancer cells [43]. Cerezo-Guisado et al found that EGCG could inhibit the proliferation and metastasis of colon cancer HT-29 cells by down-regulating the expression of AKT [44]. In T24 bladder cancer cells, EGCG treatments lead to the enhancement of apoptosis by modulation of Bcl-2 family and inhibiting PI3K/Akt pathway [45]. Cyclin and cyclin dependent protein kinase (CDK) are the essential factors of cell cycle. EGCG was demonstrated to be effective in inducing cell cycle arrest by decreasing the expression of CDK D1 protein and increasing p21 and p27 expression, and then induced cell cycle arrest and inhibited the proliferation of colorectal and liver cancer cells [46-47]. In addition, EGCG can also interfere with the WNT, IGF-1 pathway, inhibition of methyl transferase and telomerase activity in tumor cells.

Effect of EGCG on Liver Cancer

The effects of EGCG are widely studied for cancer prevention and treatment in various cancer types [48]. This part focused on the current ongoing clinical trials and scientific research studies of EGCG on liver cancer.

Clinical trial

A clinical trial was conducted to investigate the preventive effect of green tea polyphenols against the high-risk hepatocellular carcinoma. 124 individuals were included in the trial and randomized into three groups: placebo, 500mg and 1000mg green tea polyphenol capsules groups. During the treatment, the urine samples of participants were collected and the urinary 8-hydroxydeoxyguanosine (8-OHdG) levels were analyzed. The results showed that tea polyphenol can decrease the level of 8-OHdG and then suppress the DNA damage [49].

In vivo studies

The efficacy of EGCG in liver cancer was also elucidated in animals. Darweish et al found that rats with hepatocellular carcinoma (HepG2) treated with EGCG resulted in the suppression of tumor growth and metastasis to liver [50]. Hashimoto et al found that methylation (3" position) of EGCG inhibited activity of VEGF receptor 2 and p42/44 MAPK and inhibited cell proliferation and tube formation. Administration of EGCG at a low dose (1.1 mg/kg i.p. 8.3 mg/kg p.o.) suppressed tumor growth in xenografted Huh7 hepatoma mice by 50%. EGCG also reduced visualized blood vessels in tumors by 18%, suggesting high antitumor activity of EGCG via inhibition of angiogenesis [51]. Sur et al., demonstrated that EGCG could restrict the development of hepatocellular carcinoma at 30th week of carcinogen application showing potential chemoprevention in continuous treated group (mild dysplasia) followed by pretreated (moderate dysplasia) and therapeutic efficacy in posttreated group (mild dysplasia), and this restriction of liver carcinogenesis by EGCG was due to reduction in hepatocyte progenitor cell/stem cell population along with modulation of Wnt/Hh pathways [52]. Besides, Huang et al found that oral administration of EGCG at 5, 20 and 40 mg/kg to BALB/c mice with established leukemic resulted in increase of the cluster of T cell, B cell and macrophages, and promoted the phagocytosis of macrophages and promoted natural killer cell activity at 40 mg/kg, increased T-cell proliferation at 40 mg/kg [53]. In addition, EGCG was reported to be effective in increasing the sensitivity of doxorubicin in hepatocellular carcinoma in murine model. The combination of EGCG with doxorubicin greatly inhibited tumor growth, and the inhibition percentages of tumor reached as high as 65%, which was much better than the group used doxorubicin alone. EGCG was shown to be effective in increasing the intracellular doxorubicin accumulation and thus worked synergistically in inhibition of tumor growth [54]. Furthermore, hepatic metastasis was shown to be inhibited by a micronutrient mixture, including green tea polyphenol. The athymic nude mice with the B16FO melanoma cells were divided into control group and treatment group (fed with dietary green tea polyphenol mixture). After treatment, the spleens and livers in control group were exhibit large black size with metastasis nodules, while the treatment group with green tea polyphenol mixture supplement was shown less hepatic metastasis, and the percentage of liver metastasis in treatment group was reduced by 55% as compared to the control [55].

In vitro studies

Animal and clinical studies reveal cancer prevention effects of EGCG in liver cancer. EGCG also inhibits cell growth, migration and induces cell cycle arrest and induced apoptosis in hepatocarcinoma cell lines. Godeke et al proved that EGCG treatment resulted in the inhibition of HB cell proliferation, and also activated the mitochondrial intrinsic apoptotic pathway and Wnt signaling, as the Caspase 3 and proteolytic cleavage of PARP, and MYC and CCND1 were decreased [56]. Zhang et al demonstrated that EGCG induced apoptosis and promoted G0/G1 phase cell cycle arrest in hepatocellular carcinoma LM6 cells by down-regulated Bcl-2 and NF-κB expression, but no obvious effect was shown in non-cancerous liver cells HL-7702 [47]. Luo and Lin studied the anti-proliferation and cell cycle arrest effects of EGCG on HepG2 cells. They found that HepG2 cells treated with EGCG at 100 μM resulted in the increasing of G1 phase cells from 33.8% to 57.2%, and the decreasing of G2 phase cells from 34.3 to 11.9%. EGCG also enhanced the p53 and p21/WAF1 protein expressions, and thus promoted the cell cycle arrest of G1 phase of HepG2 cells [23]. Darweish investigated the chemopreventive and hepatoprotective effects of EGCG in hepatocellular carcinoma both in vivo and in vitro. They found that EGCG increased the animal survival and decreased both α-fetoprotein and HepG2 viability. EGCG ameliorated fibrosis and massive hepatic tissue breakdown, and reduced expression of MMP-9, syndecan-1 and FGF-2 both in vivo and in vitro, indicating that EGCG had chemopreventive and hepatoprotective effects against hepatocellular carcinoma via vascular invasion. [57]. Shen et al elucidated that EGCG inhibited hepatocellular carcinoma HepG2, SMMC7721 and SK-hep1 cell growth by affecting the cell cycle and induced apoptosis in these cell lines and downregulating PI3K/AKT activity [58]. Besides, there are also studies showed that EGCG inhibited hepatocarcinoma cell migration and invasion. Zhang et al revealed that EGCG induced apoptosis and inhibited the metastasis of HCCLM6 cells. The anti-metastatic effects of EGCG were associated with the inhibition of MMP-2 and MMP-9 activity. The expression levels of FUBP1, HSPB1, CH60 and NPM proteins, which are associated with metastasis, were significantly altered in the EGCG-treated HCCLM6 cells [59]. Maruyama et al found that EGCG suppressed angiogenesis and induced apoptosis in liver metastases from colorectal cancer without body weight loss or hepatotoxicity, and the liver metastatic area was significantly reduced by EGCG administration [60]. In addition, EGCG induced modulation of cell deadhesion and migration on thermo sensitive poly-(N-isopropylacrylamide) in HepG2 cells [61]. Darweish et al reported that EGCG treatment caused the reduction of superoxide anion, MPO and MDA in a dose dependent manner, and also induced apoptosis and inhibited migration in HepG2 cells [50]. Huang's results strongly suggest that EGCG can inhibit CBR1 activity and enhance the effectiveness and decrease the cardiotoxicity of the anticancer drug Daunorubicin [62]. Besides, Epigallocatechin-3-gallate sensitizes hepatocellular carcinoma Hep3B cells to 5-FU antitumor activity, and the combination of EGCG and 5-FU exhibits synergism in chemo-resistant cancer cells [63]. Liang et al demonstrated that EGCG at non-toxic doses can augment DOX-induced cell killing and sensitize chemoresistant hepatocellular carcinoma cells to DOX. The chemo sensitizing effect of EGCG may occur directly or indirectly by reversal of multidrug resistance, involving the suppression of MDR1 expression, or by enhancement of intracellular DOX accumulation, involving inhibition of P-gp function [64].

Conclusion and Future Direction

Green tea is the well-known beverage worldwide, and contributes a lot to people's health. EGCG was found to be the most abundant and bioactive regent in green tea, which showed potent anti-cancer efficacy without obvious damage to normal cells. EGCG is also demonstrated to have comprehensive protective effects, such as anti-oxidation, anti-obesity, anti-diabetes, and cardiovascular protective effects. Nowadays, most medicine drugs available for cancer treatment are very expensive, toxic or damage people's health. Thus the natural products with potential anti-cancer and comprehensive effects need more investigation and acknowledgement. This review focuses on the mechanisms of action of EGCG, and the previous and current ongoing clinical trials and scientific research studies of EGCG in liver cancer. EGCG inhibits cancer cell proliferation, induces apoptosis and cell cycle arrest, inhibited metastasis and angiogenesis, and then block cancer progress. Besides, we enumerate the clinical trial, in vivo and in vitro studies of EGCG in liver cancers, and these investigations revealed that EGCG is a potent natural medicine in preventing and treating of cancer. In addition, EGCG can work in combine with clinical chemotherapies, like DOX, 5-FU or cisplatin, to work as a sensitizer to enhance the anti-cancer effect of clinical drugs. Future studies not only need the fully elucidation of the molecular mechanisms of EGCG, but also more design strategies to develop EGCG as better chemo preventive agent for cancer treatment. This review holds promise for further application of EGCG as a potential anticancer supplement against liver cancer either used alone or in combination with other therapeutics.

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