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Review Article

Chemopreventive and Chemosensitizing Effects of Green Tea: An Evidence-based Review

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ABSTRACT

Cancer is a major health problem and second foremost cause of death globally. Chemotherapy either targeted or non-targeted is pervasive in the treatment of cancer but due to continuous and repeated doses, cancer cells develop resistance against these chemotherapeutic drugs through multiple mechanisms including MDR1 gene expression. EGCG (Epigallocatechin-3-Gallate) is one of the major polyphenols present in the dry leaves of green tea plant *(Camellia sinensis)*. It has been observed to potentiate the apoptosis and also inhibit cancer cell growth by affecting various signaling molecules and cell cycle regulatory proteins. Clinical studies demonstrated that EGCG treatment of different type of cancers has synergistic effect in combination treatment with other common clinical drugs (cisplatin, taxol, doxorubicin and vinblastine) by modulating chemotherapy response to cancer cells as compared to clinical drugs alone. This review enlightens the possible mechanisms by which EGCG overcome chemo-resistance and recover efficacy of many clinical drugs in various human cancers.

INTRODUCTION

Despite recent innovation in cancer treatment, there is a gradual increase in cancer incidence as well as cancer associated deaths worldwide (Siegel *et al*., 2016). According to the World Cancer Report, 2014, about 5.3 and 4.7 million men and women developed malignant tumor, respectively, while 6.2 million people died from cancer (McGuire, 2016). In 2012, about 14.1 million new cancer cases and 8.2 million deaths were reported worldwide (Ferlay *et al*., 2015; Khan *et al*., 2015). In men, caner incidence were estimated about 4% higher than in women (Siegel *et al*., 2016). Likewise, 18.1 million new cases and 9.6 million cancer related deaths were reported globally of which over one-half occurred in Asian countries in 2018, where about 60% of the global population is residing (Bray *et al*., 2018). According to the cancer statistics 2017, most of the deaths are due to cancer of lungs and bronchus, colorectum and prostate in men; and lung and bronchus, breast and colorectum in women (Siegel *et al*., 2016).

Chemotherapy is pervasive for treating different cancers, but unfortunately, it fails in most cases due to the development of drug resistance (Xi *et al*., 2015). The important mechanisms that protect cancerous cells from the toxic effects of anticancer drugs include multidrug efflux pumps or MDR pump in cell membrane, phase I neutralizing enzymes like cytochrome p450, and phase II detoxifying enzymes (Foygel *et al*., 2015). MDR is actually a phenomenon of tumor becoming resistant to structurally and chemically unrelated anticancer drugs. Mechanism of MDR to anticancer drugs include pharmacokinetic changes, tumor microenvironment and cell specific factors such as drug inactivation, increased drug efflux, decreased drug influx, drug targeted alterations, DNA damage repair, apoptotic evasion, epithelial-mesenchymal transitions and tumor cell heterogeneity inheritance. The increasing prevalence of drug resistance against cancer requires further advanced research and treatment development (Holohan *et al*., 2013; Wen *et al*., 2017).

Neutraceuticals are natural active substances extracted from plants and animals. They are used in appropriate pharmaceutical fashion having potential of prevention therapies for many different kinds of diseases and boosting the therapeutic action of clinical drugs according to perfect

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clinical adequacy and hence can be included in the daily diet before the clinical therapy (Bajaj and Manchanda, 2019; Nair *et al*., 2010). Tea is one of the most widely consumed drinks in the world and non- fermented green tea is more significant and effective in cancer preventive measures. Dried leaves of the plant *Camellia sinensis* are used to make green tea (Neyrinck *et al*., 2017). Approximately, 20% of dried tea manufactured worldwide is green tea (Liang *et al*., 2010). Jówko (2015) reported that green tea is associated with many health benefits and effective in preventing many diseases in association with free radicals and reactive oxygen species such as cancer, neurodegenerative and cardiovascular diseases. The main components of green tea associated with medicinal effects are flavonoids and catechins which account for about 80-90% of total flavonoids of green tea (Reygaert, 2018) and about 10-35% of the total dry weight of leaves. Epigallocatechin-3-gallate (EGCG) is the most abundant catechin in green tea that accounts for 50-70% of all others green tea catechins (Neyrinck *et al*., 2017), followed by epigallocatechin (20%), epicatechin-3-gallate (14%) and epicatechin (6%) (Reygaert, 2018). A cup of green tea containing about 2.5 g dried leaves may contains 90 mg of EGCG (Khan *et al*., 2015a; Li *et al*., 2018).

EGCG is key chemopreventive agent and acts as a modulator of tumor cells response to chemotherapy by inhibiting cancer's growth, invasion, metastasis and angiogenesis by inducing cell cycle arrest and apoptosis through multiple mechanisms (Azam *et al*., 2004; Hu *et al*., 2015; Proniuk *et al*., 2002).

Matrix metalloproteinases (MMPs) are the major contributing factor in metastasis of cancer. About 0.1-1μM EGCG is sufficient to inhibit the action of matrix metalloproteinase and angiogenesis. While concentration range of EGCG needed to inhibit cell proliferation in cancer is about 20-100μM which was observed to be much higher in the blood of the green tea consumers. But the responses of different individuals to different types of cancers vary with the concentrations (Flores-Pérez *et al*., 2016).

The aim of this review was to evaluate augmenting efficacy of one of the major green tea catechins, EGCG in combination with conventional chemotherapeutics in various human cancers. Moreover, we discuss the possible mechanisms implicated in synergism between EGCG and clinical anticancer drugs.

EPIDEMIOLOGICAL STUDY

In order to evaluate direct effect of green tea consumption on various cancer types in different populations, many cohort studies were conducted. In Japan, a very significant drop in biliary tract cancer was observed in more than 140,000 participants which was because of EGCG in green tea (Makiuchi *et al*., 2016). Similar results of reduction in cancer risks have been observed in Asian population (Liu *et al*., 2016). Meta-analysis of cohort studies demonstrated the protective effects of green tea intake on liver cancer (Ni *et al*., 2017; Sing *et al*., 2011), gastric cancer (Zhou *et al*., 2008), colorectal cancer (Sun *et al*., 2006), and ovarian cancer risks (Lee *et al*., 2013). Recently, it has been reported that a smoking person can find long term protective effects from lung cancer if one takes 7.5g of green tea on regular basis (Zijun *et al*., 2019). Likewise in another cohort study, it was revealed that intake of more than three cups of green tea per day provides antagonistic effect on breast cancer (Ogunleye *et al*., 2010; Sun *et al*., 2005). With average follow up of 13.3 years of Japanese population of age (40-70years), a cohort study provided evidences about protective effect of green tea consumption on acute myeloid and follicular lymphomas (Takada *et al*., 2019). It has also neuroprotective effect and showed inverse effect for risk of glioma (Cote *et al*., 2019).

MECHANISM OF SYNERGY BETWEEN EGCG AND ANTICANCER DRUGS

There is a diverse range of mechanisms by which EGCG could promote apoptosis including generation of reactive oxygen species (ROS), inhibition of survival pathways like Janus kinase/signal transducer and activator of transcription factor 3 (JAK/STAT3), nuclear factor-κB (NF-κB) and Akt signaling pathways, down-regulation of survivin gene expression, and activation of caspases (Hagen *et al*., 2013). The epidemiological, preclinical and laboratory research reports showed an inverse association between tea consumption and risk of multiple cancer types (Hu *et al*., 2015; Shafique *et al*., 2012).

Lung and liver cancer

The most common and aggressive cancers with survival less than one year after diagnosis and treatment is lung cancer. It accounts for 11.6 % of the total new cancer cases and 18.4% of the total cancer deaths globally as estimated by GLOBOCAN 2018 report (Bray *et al*., 2018). According to 2012 data, out of 14.1 million overall cancer cases, 1.82 million were diagnosed as lung cancer and 1.6 million deaths were calculated while 782,000 new cases and 745000 deaths due to liver cancer were estimated. This survival possibility depends upon the tumor stage and liver functioning (Ferlay *et al*., 2015; Liang *et al*., 2010). Clinical effects of chemotherapy to the cancer mostly constrained

due to resistance to the clinical drugs. To overcome this problem, various treatments such as combination therapy have been used but overall satisfactory results have still not been obtained.

Cisplatin (Cis) is a platinum based alkylating agent with therapeutic success against lungs, bladder, testicular, ovarian, colorectal and head and neck cancers. The best therapeutic response of Cis is characterized by DNA damage and mitochondrial apoptosis. A plethora of changes contribute in the development of resistance in cancerous cells against Cis somehow including the reduction of its intracellular accumulation by down-regulation of copper transporter protein 1 (CTR1), up-regulation of multidrug resistant proteins (MRPs), inhibition of p38 MAPK pathway and also through increasing glutathione (GSH), and other cytoplasmic 'scavengers' having nucleophilic properties leading to therapeutic failure (Galluzzi *et al*., 2012).

Exploring novel bioactive molecules which could sensitize cancer cells to Cis are highly desirable. EGCG has an anti-angiogenesis potential and multiple effect on vascular endothelial growth factor (VEGF), MMP-9, angiopoietins (ANGs) and platelet-derived growth factor (PDGF) to reduce the cancer metastasis. Co-treatment of Cis and EGCG significantly reduced the growth of A549 lung cancer cells by rebalancing of vascular growth factors (Peng-Bo *et al*., 2013). To decipher the augmenting efficacy to EGCG, A549 and H460 lung cancer cells were made resistant to Cis by gradual exposure to Cis. Synergistic anticancer effect was observed when Cis resistant cells were treated with Cis (30 μM) + EGCG (80 μM) (Jiang *et al*., 2016; Kim and Lee, 2014). Cell cycle arrest through inhibition of cyclin D1 and proliferation by suppression of NF-kB was observed in A549 cells with same co-treatment (Singh *et al*., 2015).

In another study, Jiang *et al*. (2016) investigated the augmenting effect of EGCG in multiple lung cancer cells including A549, H460 and H1299 cells. The study showed that EGCG augmented the anticancer activity of Cis by increasing accumulation of Cis in the cells through the Nuclear enriched abundant transcript 1 (NEAT1)-mediated increased expression of CTR1. Moreover, the localization of CTR1 was also observed in the cytoplasm instead of peri-nucleus after EGCG treatment where its ability in transportation of Cis increased. In-vivo confirmation was done which also showed the reduced tumor volume and body weight in model animal by dose additive effect (Jiang *et al*., 2016).

Paclitaxel or taxol is a mitotic inhibitor which is being used in cancer clinics for various solid tumors. Mechanistically, its antitumor effect is attributed by its ability to induce G2/M phase cell cycle arrest by stabilizing the microtubules with β-tubulin subunit (Blagosklonny *et al*., 1999; Dumontet and Sikic, 1999). To observe additive or synergistic effect of EGCG with paclitaxel, Park *et al*. (2014) performed very interesting experiments in H460 lung cancer cells. First of all, authors investigated the effect of concurrent therapy of EGCG and paclitaxel and found low cytotoxic effect compared to paclitaxel treatment as monotherapy. However, a synergistic effect was observed when EGCG was administered to cells pretreated with paclitaxel for 24h. The synergy was observed in term of decreased expression of Bcl-2 and pro-caspase-3 and increased expression of 89 kDa PARP.

Doxorubicin (DOX) is an important member of chemotherapeutic anticancer drugs used against various solid tumors (Maryam *et al*., 2017). Its anti-tumor mechanism involved DNA intercalation, topoisomerase-II inhibition, and ROS generation. (Gewirtz, 1999). Despite potent anticancer activity of this drug on one hand, it induces the expression of p-glycoprotein (P-gp) one the other hand, that plays a key role in development of MDR by actively exporting a wide range of drugs out of cells (Khan *et al*., 2015a). In addition, DOX has been reported to activate various survival signaling pathways which could also contribute in drug resistance phenomenon (Satonaka *et al*., 2017).

It was found that EGCG+DOX co-treatment attenuated survival of DOX resistant BEL7404 cells of hepato-caricinoma by reduction in hypoxia inducing factor (hif-1α) and MDR1(p-glycoprotein) expression (Wen *et al*., 2017). A reduction of 51.1% in the survival rate of BEL-7404/DOX resistant cells was found as compared to BEL-7404 parent cells with Dox (0.8mg/ml) and EGCG (60mg/ml) treatment. The findings were further validated using *in vivo* animal cancer model (Liang *et al*., 2010). Similar results were monitored when EGCG treatment to the paclitaxel in H460/PT cell line of lung cancer significantly enhanced the accumulation of rhodamine-123 and reduced the expression of MDR1 gene to induce the paclitaxel sensitivity in the H460/PT cell (Xi *et al*., 2015). It was reported in another study that EGCG has potential to inhibit the overexpression of DOX-induced p-gp and potentiate the intracellular accumulation of rhodamine-123 about 15% in DOX resistant HepG2 cells after treatment with EGCG (50μM) and DOX (3μM) as compared to DOX alone. Additional experimental investigations proved that DOX induces expression of p-gp by activating PI3k/akt and MEK/ERK survival signaling pathways while EGCG reverses the effect of DOX by inhibiting the activation of aforesaid signaling pathways (Satonaka *et al*., 2017).

Breast cancer

It is the second major and the most commonly

diagnosed cancer in women. It accounted for 11.6% (2.1 million) new cancer cases out of all the cancer cases recorded in 2018 (Bray *et al*., 2018). It ranked 5th as a cause of death worldwide in 2012 (Ferlay *et al*., 2015). More than 200,000 of breast cancer cases were annually diagnosed in the US and is the second leading cause of women's death (Moore-Smith *et al*., 2018). Miller *et al*. (2016) estimated that more than 3.5 million women in the US have invasive breast cancer history. It was expected that breast cancer alone accounts for about 30% of all the newly diagnosed cancers in women. It is interesting, and somewhat surprising to know that the drop in breast cancer mortality rate is greater during younger age (under age 50) (Carioli *et al*., 2017).

Contrary to its regulated expression in normal cells, constitutive activation of Nrf2 has been detected in many cancers which protects the cancer cells from the cytotoxic effects of anticancer drugs (Foygel *et al*., 2015). NE-F2 related factor-2 (Nrf2) is a transcriptional factor which is bound with a repressor Keap1 and kept in the cytosol in inactive form. When cell is under stress such a oxidative stress, Nrf2 is phosphorylated and translocated into nucleus where it induces the transcription of phase-II detoxifying enzymes which play vital role in protecting the cell from oxidative stress, mutagenesis and tumorigenesis. So, Nrf2 act as gatekeeper to protect cells from several stress induced malady by activating various downstream genes like quinone reductase, UDP-glucuronosyl transferases, glutathione S-transferase, gamma-glutamylcysteine synthetase, epoxide hydrolase and heme oxygenase (HO). The use of antioxidants to boost the Nrf2-dependent adaptive response has emerged to be a promising strategy for cancer prevention. Different combinations of chemotherapeutic drugs and antioxidants exhibit different functions in cancer cells including growth inhibition or survival benefits. The same effect of EGCG in combination with Cis and 5-Fluorouracil (5-FU) has been investigated in MDA-MB-231 breast cancer cells. EGCG potentiated the anticancer activity of both clinical drugs in a synergistic fashion in in vitro cell culture and in vivo mouse model study (Foygel *et al*., 2015).

Taxol and vinblastine are microtubules targeting chemotherapeutic agents that arrest the cell cycle at G2/M phase. It is well known now that taxol and vinblastine induces the expression of cyto-protective chaperon glucose-regulated protein 78 (GRP78) which inhibits the activation of various pro-apoptotic proteases such as caspase-4 and -7 and thus leads to development of drug resistance (Wang *et al*., 2009). Since EGCG is a potent inhibitor of GRP78, researchers have evaluated the resistance reversal effect of EGCG in breast cancer cells. EGCG in combination with taxol remarkably suppressed the growth of 4T1 and MDA-MB-231 cancer cells compared to taxol treatment alone. By in-vivo confirmation on 4T1 cell line, a significant reduction in tumor weight and volume by taxol (10mg/kg) and EGCG (30mg/kg) treatment was observed (Luo *et al*., 2010). The additional literature indicated that EGCG (10μM) along with vinblastine (0.1μM) or taxol (0.5μM) treatment led to knockdown of GRP78 and potentiated the expression of JNK by phosphorylation of caspase 7 and PARP cleavage led to increased apoptotic rate about 15% in MCF-7 cells. The same in vitro treatment was found to reduce the colony survival about 34% with vinblastine and 40% with taxol in combination to EGCG. It was found that the treatment of taxol and vinblastine induced JNK and caspase-7 expression by EGCG. It increased the sensitivity of breast cancer to vinblastine and taxol resulted in enhanced cytotoxicity (Wang *et al*., 2009).

From the shell nanoparticle, the sequential release of EGCG after taxol in MDA-MB231 cells sensitized them to taxol. About 65% reduction in cell viability was reported by an experiment with (100 μM) EGCG and taxol (10 nM) treatment due to suppressing the NF-ƘB relative expression about 0.7 folds and arresting the cell cycle by increasing the transcription of p21 gene. The reduction in taxol efflux in the cancer cells was observed by the same treatment via 13.5 folds reduction in ABCB1 gene expression and about 8 folds p-gp gene expression (Narayanan *et al*., 2015). MDA-MB231 cell line has highly invasive nature and metastasized by matrix metalloproteinase (MMPs) through breakdown of extracellular matrix during tissue remodeling. This is targeted by inhibition of MMP2 and MMP9 expression and their activity averaging780 pg/ml and 35% respectively and inhibiting the cells viability about 40% by Taxol (10 μM) and EGCG (50μM) co-treatment as compared to taxol monotherapy (Ramadass *et al*., 2015).

Doxorubicin is an antineoplastic and cytotoxic chemotherapeutic drug proved to be effective to treat breast cancer (Li *et al*., 2018). To assess the effect of EGCG on reversal of DOX resistance in breast cancer, a DOX resistant cell line ($MCF7/DOX_{500}$) was established. This cell line was characterized by high expression of matrix metalloproteinases (MMP2 and MMP9). The treatment with 20 μM EGCG in combination with 120μM of gallic acid highly reduced their proliferation and invasion by significantly suppressing MMP9 and MMP2 expression (Nowakowska and Tarasiuk, 2016).

Prostate cancer

Prostate cancer is the second most common type of cancer and 5th leading cause of death in men. From 2012 cancer report, it was found that about 1.1 million prostate cancer patients were diagnosed globally (Ferlay *et al*.,

2015). The more occurrence of prostate cancer was seen in age group of 55-69. Prostate cancer identification is mostly done by prostate-specific antigen (PSA) testing (Miller *et al*., 2016; Weiner *et al*., 2016).

Mitochondria play a central role in implicating the cellular apoptosis by activation of capsase proteases. These proteases cleave many different proteins leading to induction of rapid apoptotic cell death. Caspase 9 is a key player in mitochondrial apoptotic pathway. Caspase 9a and caspase 9b are the two spliced isoforms of caspase 9. Caspase 9b act as anti-apoptotic against apoptotic caspase 9a (Hagen *et al*., 2013). In an vitro study, EGCG (25µM)+Cis (2.5µM) treatment resulted in induction of apoptosis in PC3 prostate cancer cells in a synergistic fashion. Combination therapy enhanced apoptosis by down-regulating Bcl-2 and increasing caspase 9a/9b ratio about 5 folds higher compared to monotherapy of Cis. (Hagen *et al*., 2013; Ping *et al*., 2010). Similarly, EGCG enhanced the chemosensitivity of docetaxel in androgen-independent prostate cancer cells. EGCG when used in combination with quercetin, it increased the cytotoxicity of docetaxel by 3-fold in LAPC-4-AI cells and 8-fold in PC3 cells. The antitumor activity was derived from G2/M phase arrest and induction of apoptosis. Moreover, this combination inhibited the activation of PI3k/akt and STAT3 signaling pathways which are vital for survival benefits and development of chemo-resistance in cancer cells (Wang *et al*., 2015; Zhao *et al*., 2016).

Laminin receptor (67 LR) is a protein strongly associated with the proliferation and progression of many cancers including prostate cancer. Its overexpression in the neoplasm is the indication of metastatic aggressiveness (Pesapane *et al*., 2017). DOX and EGCG packed gold nano-particles (DOX-GLT/EGCG AuNPs) were found to reduce the 67 LR mediated delivery of DOX in PC3 cell line. MMP2 triggered the DOX release from these nano-particles to improve the rate of apoptosis by synergic inhibitory effect of EGCG (Tsai *et al*., 2016).

Colorectal cancer

Colorectal cancer (CC) is the 3rd most commonly diagnosed cancers and ranked 2nd in term of mortality. About 1.8 million new cases of CC were recorded in 2018 (Bray *et al*., 2018). According to 2012 report, from 14.1 million overall cancer cases, 1.36 million were diagnosed as CC (Ferlay *et al*., 2015).

Autophagy is a homeostatic or self-degradative process of degradation of intracellular proteins or organelles by the lysosomes and is capable of killing drug resistant cells in which the apoptosis is not possible (Amaravadi *et al*., 2016). The chemosensitizing effects of EGCG were investigated in DLD1 and HT-29 CC cancer cell lines in combination of clinical drugs. EGCG promoted the antitumor effects of Cis and oxaliplatin by inducing autophagy rather than apoptosis as could be seen from increased expression of LC3-II and decreased expression of LC3-I. Moreover, the rate of autophagic cell death by combination treatment was significantly higher compared to monotherapy of clinical drugs (Hu *et al*., 2015).

Many studies showed that vinblastine is weakly absorbed by intestinal barriers. It was reported that by 100 µM EGCG treatment, an increase in vinblastine accumulation was observed on $Caco_2$ colon cancer cells. Thus the passage of vinblastine through intestinal barriers and its uptake by cells increases in the presence EGCG without affecting the integrity of this barrier (Jodoin *et al*., 2002). It was believed that ABC transporter potentiate the efflux of drug from the cells leading to multidrug resistance development. So, sensitivity of polyphenol to resistant cells caco2 was observed to be 7 times higher than the HCT116 cells by showing the synergistic effect with DOX in caco2 cells (Li *et al*., 2018).

Ovarian cancer

Ovarian Cancer (OC) is in top ten most commonly diagnosed cancers and ranks in top five deadliest cancers in most countries. In 2015, OC was diagnosed in 1.2 million women and caused 161,100 deaths worldwide. In the 21st century, it was estimated that a woman's overall lifetime risk of developing OC is about 1.6% and her chance of dying because of this disease is 1/100 (You *et al*., 2018). New estimated cases of occurrence and death of OC in United States in 2016 were 22,280 and 14,240, respectively (Siegel *et al*., 2016).

Cis is one of the most promising anticancer drugs used in cancer clinic for the treatment of various cancers including OC. The anticancer mechanism involves DNA alkylation, promotion of oxidative stress and induction of apoptosis. However, emergence of cisplatin resistance has become the major challenge in treatment of various cancers including OC (Chan *et al*., 2006). EGCG has been reported to enhance anticancer efficacy of Cis by different mechanisms. Chan *et al*. (2006) have reported that combine treatment of ovarian cancer cells with EGCG+Cis is a promising strategy to overcome Cis resistance in OC. EGCG potentiated the toxicity of Cis in CAOV3, SKOV3, and C200 ovarian cancer cells to different degrees in a dose-dependent fashion. For example, SKOV3 cells showed insensitivity to Cis at 2µg/mL while pre-treatment of SKOV3 cells with 7.5, 15, 22.5, and 30 µM EGCG inhibited the growth of cells by 8.7, 26.6, 59.8, and 90.8%, respectively. A similar chemosensitizing trend of EGCG was observed in CAOV3 C200 cells against Cis (Chan *et al*., 2006). The molecular mechanism implicated in

EGCG mediated sensitization was found to be linked with increased level of H2O2. In addition, Chen *et al*. (2013) investigated the chemo-sensitizing efficacy of EGCG in Cis resistant A2780/cp20 OC cells. EGCG+Cis treatment enhanced the anticancer activity of Cis by inducing G2/M phase arrest and promoting apoptosis.

The published data from other research report indicate that green tea polyphenols could overcome multi-drug resistance in OC by interacting with p-glycoprotein. CH^RC5 are vinblastine resistant OC cells with higher expression of p-gp. The IC50 of vinblastine against CH^RC5 cells was 1000nM while in the presence of 50µM EGCG, the IC50 of vinblastine was decreased to 9nM. (Jodoin *et al*., 2002).

Further literature survey indicated that EGCG could improve sensitivity of OC cells (OVCAR3 and SKOV3) to Cis by inducing expression of copper transporter 1 (CTR1) which led to increased accumulation of Cis inside the cells and Cis-DNA adducts, thereby inducing apoptosis. The findings were further validated by in vivo study (Wang *et al*., 2015)

Cervical cancer

Cervical cancer is the most common gynecological malignant tumor, and its incidence rate is at fourth ranking in female malignant tumors. In 2012, there were 527,000 new cases of cervical cancer worldwide while 265,000 women died because of this disease, of which 83% of cervical cancer occurred in developing countries (Qiao, 2018).

A study was conducted on HeLa cell of cervical cancer to assess the synergism between Cis and EGCG. Combined treatment of both these drugs (Cis 250nM + EGCG 25µM) exhibited synergistic effect in cervical cancer cells. The underlying mechanism in this synergism was found to be linked with the potential of EGCG to inhibit survival pathways and promoting apoptosis. EGCG sensitized Hela cells to Cis by inhibiting NF-kB, COX-2, Akt and mTOR pathways which are considered vital for growth of cells expression. Moreover, EGCG reduced Cis induced oxidative stress by enhancing Nrf2 expression (45 folds) and HO-1 expression (Kilic *et al*., 2015).

Cell cycle arrest at sub-G1 stage in the Hela and SiHa cells was reported by Cis (4µ M) and EGCG (11µM) treatment which decreased the cell viability about 40% compared to the cells treated with Cis alone (Singh *et al*., 2013, 2015). Cell proliferation was also found in Hela and SiHa cells to be inhibited significantly due to this combine treatment. Mitochondrial membrane potential disruption was observed with release of cytochrome c in the cytosol. The expression of Bcl2 was found to be down-regulated while the expression of p53 and Bax was upregulated. The induction of caspases activation and PARP cleavage; and increase in lipid peroxidation, intracellular ROS generation and inhibition of GSH, in cervical cancer cells was observed in combination therapy. The inhibition of Cis induced Nf-kB activation resulted in down regulation of cyclin D1 expression in treatment of both EGCG and Cis as compared to Cis treatment only (Singh *et al*., 2013).

Leukemia

Leukemia comprises of a group of malignancies and is responsible for 8% of all cancer types. It was diagnosed in 2.3 million people according to 2015 report. It occurs in all age groups. It is the most common type of malignancy in children and accounts for 30% of all cancers in children (under 15). In 2012, over 350,000 new cases were diagnosed. The treatment options for leukemia include chemotherapy, radiation therapy and bone marrow transplantation (Kouhpeikar *et al*., 2019). Chemotherapy of the leukemia can be improved and kept protected from development of drug resistance by combination treatment of antioxidant polyphenol i.e. EGCG.

It was reported that cytotoxicity of Cis was found to be reduced due to development of resistance against this drug in THP-1 cells. Treatment of EGCG (3.25 µM) increased the cytotoxicity of Cis (20 µM) about 60%. Cis is reported to enhance the NF-KB activation in THP-1 cells. However, when cells were treated with Cis+EGCG NF-KB activation was significantly suppressed (Singh *et al*., 2015). In addition to overcoming NF-KB activation, EGCG has been reported to exhibit synergism in leukemia cells by inhibiting the expression of p-gp. It was observed that CCRF-CEM cells with low expression of p-gp are more sensitive to EGCG than CEM/ADR5000 DOX resistant cells with high expression of p-gp. Additional data showed that EGCG enhanced the cytotoxicity of DOX in by inhibiting the expression of p-gp and increasing intracellular accumulation of DOX (Li *et al*., 2018).

Renal cell carcinoma

Renal cell carcinoma (RCC) is most lethal type of human malignancies in urological system. Worldwide, RCC was ranked as 6th most frequently diagnosed cancer in men and 10th in women, accounts about 5% and 3% of all oncological diagnosed cases in men and women, respectively. According to the most recent data provided by the WHO in 2012, over 140,000 RCC-related deaths recorded annually ranking as the 13th most common cause of cancer death globally (Capitanio *et al*., 2019).

Connexin 32 gene is one the most important tumor suppressor genes and a gap junction protein that control the growth and differentiation of cell through mediating the cellular communication. It was reported that impaired

expression and loss of function of connexin 32 resulted in the development of cancer. In renal cell carcinoma, connexin 32 gene is silenced by epigenetic modifications. Hypermethylation in CpG islands of promoter region of a gene results in silencing of a gene. Hypermethylation has been detected in promoter of connexin 32 gene which is considered important in renal cell tumorigenesis. When the Caki-1 renal cancer cells were treated with EGCG (2.5 µM) and vinblastin (20µM), EGCG restored the expression of connexin 32 gene and increased the cytotoxicity of vinblastin. EGCG increased chemosensitivity of vinblastin by connexin 32 expression which ultimately led to suppression of MDR1 via increased inhibition of src tyrosine kinase and activation of pro-apoptotic JNK pathway (Sato *et al*., 2013).

Osteosarcoma

Osteosarcoma being the most common malignancy of bone with 5 year survival rate around 61%, accounts for about 2/3 cases of bone cancer worldwide (Di *et al*., 2017; Wang *et al*., 2017). DOX is one of the major chemotherapeutics being used to treat osteosarcoma. However, drug resistance has reduced the efficacy of this drug in osteosarcoma patients. Induction of pro-survival autophagy by DOX in cancer cells is considered one of the mechanisms of drug resistance. EGCG+DOX treatment improved the anticancer effect of DOX in a synergistic fashion in U2OS or SaoS2 cell lines. The in-depth mechanism involved in this synergy was attributed to the ability of EGCG to inhibit DOX-induced pro-survival autophagy on one hand, and stemness reduction on the other hand, by inhibiting Notch3/DLL3 signaling pathway and its downstream target gene "LncRNA SOX2OT variant 7" (Wang *et al*., 2018).

Mitochondria are the important component of a cell involved in intrinsic apoptosis executing machinery of eukaryotic cell (Khan *et al*., 2015b). The chemosensitizing effect of EGCG against Cis was also reported by other research groups in A549 lung cancer cells (Flores-Pérez *et al*., 2016: Singh *et al*., 2015). Mechanistically, EGCG improves the efficacy of Cis by depolarizing mitochondrial membrane and activation of caspase-cascade. The combine effect was noted to be additive.

CONCLUSION AND FUTURE PERSPECTIVES

Naturally occurring antioxidants like EGCG obtained from green tea provided new insights in the modification of cancer therapy. Cancer cells with diverse genetic make up are considered the most advanced cells with respect to evolutionary point of view and develop resistance against mono-targeted chemotherapeutics soon after they are exposed to these therapies. Collective data from multifarious case-control and research studies have provided substantial amount of evidence in favour of green tea consumption as a powerful chemopreventive beverage. EGCG being the major component of green tea plays vital role in chemoprevention and enhancing anticancer efficacy of clinical drugs in combination therapies through multiple mechanisms. EGCG interact directly with plasma proteins and phospholipids and stimulate the signaling pathways to control cancer cells proliferation. It is easily transported into intracellular compartments and mediates or controls certain biological process implicated in cancer. In this review, interaction of EGCG in combination with other clinical drugs such as cisplatin, taxol, doxorubicin and vinblastine has been described. We mentioned the effective concentration of EGCG in cancer prevention so that pharmacokinetics studies can be performed with the physiological outcomes. Furthermore, it might be useful as potential chemo-sensitizer which can be introduced into treatment regimen to improve the efficacy of anticancer drugs. Finally, it is worth mentioning that data of epidemiological studies on chemopreventive potential of green tea has been obtained from different countries which are accustomed to take tea without sugar. Since cancer cells mainly fulfill their energy demand from aerobic glycolysis, green tea with plenty amount of sugar may not have a protective effects against cancer.

Statement of conflict of interest

The authors have declared no conflict of interest.

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