Review Article

Cancer preventive and therapeutic effects of EGCG, the major polyphenol in green tea

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ABSTRACT

(-)-epigallocatechin-3-gallate (EGCG), the major bioactive catechin in green tea (GT) has been studied for almost past thirty years as an agent initially for its cancer chemoprevention effects and then for its cancer chemotherapeutic ability. This agent has shown considerable anti-cancer effects in a variety of preclinical cell culture and animal model systems. However, its clinical application to human patients is hampered by a variety of reasons that includes its stability and bioavailability. As a result, an increased number of studies assessing the effects derived from the use of EGCG are been employed in combination with other agents or by utilizing innovative carrier settings. Here, we summarize the current understanding of the anticancer effects of EGCG and its effects with other combinations on different kinds of cancers. Further, we also present the available information for the possible mechanism of action of EGCG.

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Introduction

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [1]. It is one of the major ailments effecting humankind and remains as one of the leading causes of mortality worldwide, for instance, above 10 million new patients are diagnosed with cancer every year and over 6 million deaths are associated with it representing roughly 12% of worldwide deaths [2]. Almost fifteen million new cancer cases are thought to be diagnosed by year 2020 [2,3] which is anticipated to be potentially increase to over 20 million by 2025 [2,4]. It is also anticipated that the growth and aging of the population might be increase the new cancer cases to 21.7 million within about 13 million cancer deaths by the year 2030 [5]. The development of cancer is a multifactorial process [6] which can
be caused by external factors such as infectious organisms, environmental pollutants, tobacco and an unhealthy diet or internal factors such as hormones, inherited genetic mutations and immune conditions may act together or singular to cause the incidence of cancer [7]. Since cancer is associated with such high morbidity and mortality worldwide, there is an urgent need to determine ways of management of this ailment where the current treatment modalities are mainly surgery, radiation based therapy, chemotherapy, gene therapy and/or hormonal therapy [2]. Natural products, especially those derived from plants, have been used to help mankind sustain its health since the dawn of medicine [8]. Nowadays, just like in ancient times, natural compounds are still determining factors in remedies [9].

Herbal medicine or Herbalism (also known as phytotherapy) is the study of botany and use of plants intended for medicinal purposes or for supplementing a diet, has been applied for thousands of years, but researchers started to study their mode of action at the molecular, cellular and tissue levels only recently [10–12]. It is also a firm belief that naturally occurring plant based natural compounds when properly formulated and administered have a key role in cancer management.

Chemoprevention, especially through the use of naturally occurring phytochemicals capable of impeding the process of carcinogenesis at one or more steps, is an ideal approach for cancer management [13]. Among natural compounds, ever since our initial work in describing its potential benefit against cancer, green tea has been extensively studied worldwide in a variety of cancer models and the resulting data has been very promising. Green tea leaves comprises of a diverse number of components (Fig. 1) that are demonstrated to be beneficial to human health. The green tea polyphenols are flavonols, commonly known as catechins [14] which are found in greater amounts in green tea than in black or Oolong tea [15].

Tea catechins were first isolated by Michiyo Tsujimura in 1929 in Japan [16] and since then four main types of catechins have been found in green tea leaves (Table 1): (-)-epigallocatechin-3-gallate (EGCG) accounts for approximately 59% of the total catechins from the leaves of the green tea, (-)-epigallocatechin (EGC) (19%), (-)-epicatechin-3-gallate (ECG) (13.6%), and (-)-epicatechin (EC) (6.4%) [17,18]. The functional and structural differences between these catechins are attributed to the number of hydroxyl groups on the B-ring (Fig. 2) and the presence or absence of a galloyl moiety [18].

Among these catechins, EGCG is the most studied and is considered to play a crucial role in cancer-preventive and therapeutic activities [19–23]. Several studies have been performed to examine the effects of EGCG on various in vitro cancer-related molecular targets and in vivo models for potential cancer chemoprevention and therapy [24]. The overwhelming majority of these studies observed that EGCG inhibits a vast array of anticancer molecular targets (Fig. 3) and cancer-related cellular processes [25].

Despite accomplished outcomes in preclinical settings, its applicability to humans has met with limited success for many reasons including inefficient systemic delivery and bioavailability. Several optimization approaches including utilization of nanoparticle based delivery of EGCG have been utilized to circumvent the issues, for instance, we in a seminal study [26] introduced the novel concept of “nanochemoprevention” that utilizes nanotechnology for enhancing the outcome of EGCG in cancer chemoprevention.

Combination therapy or polytherapy (versus monotherapy) is therapy that consumes more than one medication. There has been some emphasis on determining the effects of combining EGCG with other dietary agents. Several studies have indicated that anti-cancer efficacy and scope of action of the individual agents can be further enhanced by combining them synergistically with chemically similar or different compounds (Fig. 4). Such a
combination might be effective in reducing the drug dosage and resistance, and simultaneously exhibiting higher therapeutic outcome [27–29]. Studies suggest that EGCG can synergistically inhibit cancer cells in vitro and in vivo when combined with other dietary agents (Table 2), such as [6]-gingerol [30], curcumin [31], lovastatin [32], quercetin [33], sulforaphane [34], panaxadiol [35], and pterostilbene [36]. Some evidence is also available for combination with chemotherapeutic agents such as 5-fluorouracil [37], capecitabine [38], cisplatin [39], docetaxel [40], doxorubicin [41] and temozolomide [42], or other agents like sodium butyrate [43], vitamin C and amino acids [44]. Combination of EGCG with these molecules can synergistically inhibit cancer cell proliferation [45,46], induce apoptosis [47,48] and suppress tumor angiogenesis and growth [40] to name a few pathways that are effected by such an amalgamation. This synergistic effect, on one hand, may be associated with enhanced bioavailability of EGCG [49]. Studies find that natural small molecules, such as quercetin can increase the bioavailability of EGCG in vitro and in vivo [33]. Current literature summarize the current understanding of the anti-cancer effects of EGCG alone and in combination with other dietary and pharmaceutical agents.

### Table 1

| Molecular group | Component | Molecular Formula | MW (g/mol) | Percent of dried tea extract | Main Biological effects |
|-----------------|-----------|-------------------|------------|----------------------------|------------------------|
| Polyphenols     | Epicatechin | C_{15}H_{14}O_{6} | 290.26     | 30–42                      | Cancer prevention, antioxidant, antibacterial and antiviral effects. |
| Catechins       | Epicatechin-3-gallate | C_{15}H_{14}O_{10} | 442.37     |                            |                        |
|                 | Epigallocatechin | C_{15}H_{14}O_{7} | 306.27     |                            |                        |
|                 | Epigallocatechin-3-gallate (EGCG) | C_{22}H_{18}O_{11} | 458.375    |                            |                        |
| Flavonols       | Kaempferol | C_{15}H_{18}O_{6}  | 286.23     | 5–10                       | Anti-histamine and anti-inflammatory effects. |
|                 | Quercetin  | C_{15}H_{18}O_{7}  | 302.236    |                            |                        |
|                 | Myricetin  | C_{15}H_{18}O_{8}  | 318.2331   |                            |                        |
|                 | Theogallin | C_{14}H_{18}O_{10} | 344.27     | 2–4                        | Inhibition of Influenza A viruses. |
|                 | Chlorogenic acid | C_{15}H_{18}O_{7} | 354.31     |                            |                        |
|                 | Coumarylquinic acid | C_{15}H_{18}O_{7} | 338.312    |                            |                        |
| Organic acids   | Ascorbic acid | C_{6}H_{8}O_{6}   | 176.124    | 1–2                        | Anticancer effects. |
|                 | Gallic acid  | C_{8}H_{10}O_{4}  | 170.12     | 0.5                        |                        |
|                 | Quinic acid  | C_{4}H_{8}O_{5}   | 192.17     | 2                          |                        |
|                 | Folic acid   | C_{9}H_{10}N_{2}O_{4} | 441.404  | 0.5                        |                        |
|                 | Other organic acids | – | – | 4–5 |                        |
| Amino acids     | Theanine    | C_{6}H_{11}NO_{3} | 174.2      | 4–6                        | Neuronal cell protection and relaxation effect. |
|                 | γ-aminobutyric acid | C_{6}H_{10}N_{2}O_{2} | 103.121    | 2–4                        | Decrease of blood pressure. |
| Methylxanthines | Caffeine    | C_{11}H_{14}N_{4}O_{2} | 194.19    | 7–10                       | Increased alertness and a mild diuretic effects. |
|                 | Theobromine | C_{11}H_{14}N_{3}O_{2} | 180.164    |                            |                        |
|                 | Theophylline | C_{11}H_{14}N_{2}O_{3} | 180.167    |                            |                        |
| Carbohydrates   | Glycosides  | –                  | –          | 10–15                      | Energy and prevent blood sugar increase. |
|                 | –          | –                  | –          | 6–8                        | Regulators. |
| Minerals        | Alumimum, fluorine, manganese, iron, magnesium, potassium, phosphorus, zinc, selenium and sodium. | – | – | 6–8 | |
| Volatiles       | Saponin     | C_{20}H_{30}O_{17} | 1223.363   | 0.02–1                     | Anti-fungal, anti-inflammatory, and anti-allergy properties. |
|                 | Linalool    | C_{10}H_{18}O_{5} | 154.25     |                            |                        |
|                 | α-Cardinene | C_{10}H_{16}O_{3} | 204.357    |                            |                        |
|                 | Geraniol    | C_{10}H_{16}O_{3} | 154.253    |                            |                        |
|                 | Nerolidol   | C_{10}H_{16}O_{3} | 222.37     |                            |                        |
|                 | α-Terpineol | C_{10}H_{16}O_{3} | 154.25     |                            |                        |
|                 | Cis-Jasnone | C_{11}H_{18}O_{4} | 164.246    |                            |                        |
|                 | Indole      | C_{8}H_{11}N     | 117.15     |                            |                        |
|                 | β-Isoflavone | C_{11}H_{18}O_{3} | 192.302    |                            |                        |
|                 | 1-Octanal   | C_{8}H_{16}O     | 128.215    |                            |                        |
|                 | Indole-3-Butindol | C_{11}H_{18}O_{3} | 147.18    |                            |                        |
|                 | β-Caryophyllene | C_{13}H_{24}     | 204.36     |                            |                        |
| Vitamins        | Riboflavin (B2) | C_{11}H_{17}NO_{6} | 376.369    |                            | Maintenance of healthy skin and mucus membrane. |
|                 | Thiamine (B1) | C_{12}H_{12}N_{5}O_{5} | 265.355   |                            |                        |
|                 | Niacin (B3) | C_{12}H_{12}N_{5}O_{4} | 206.128   |                            |                        |
|                 | Vitamin B6  | C_{29}H_{50}O_{2} | 430.717    |                            |                        |
|                 | Vitamin E   | C_{29}H_{50}O_{2} | 536.888    |                            |                        |
| Chlorophyll     | –          | –                  | –          | 893.509                    | Deodorizing effect, kidney stone prevention and strengthens immune system. |

### EGGC anticancer effects

#### Induction of apoptosis

Apoptosis is a genetically encoded program leading to cell death that is involved in normal development and homeostasis throughout the animal kingdom [50]. It is the main event that is known to regulate the occurrence and/or spread of cancer [2]. The morphological characteristics of apoptosis include cell shrinkage, nuclear fragmentation, chromatin condensation and membrane blebbing [50–52]. Apoptosis can undertake one or two pathways, intrinsic and/or extrinsic pathway(s) [53]. Intrinsic pathway, also known as mitochondrial pathway, can be induced through intracellular stresses via DNA damage or oxidative stress leading to release of mitochondrial Cytochrome C to form apoptosome complex [54]. This complex is composed of Cytochrome C, apoptotic protease activating factor 1 (Apaf-1) and procaspase-9 [55], which activates Caspase-9, Caspase-3 and Caspase-7 [56]. Otherwise, extrinsic pathway or death receptor pathway can be induced by death ligands Fas ligand (FasL), tumor necrosis factor α (TNFα) and TNF-related apoptosis inducing ligand (TRAIL) [57]. These ligands
Inhibition of angiogenesis and related mechanisms

Like all cells, cancer cells require a constant supply of nutrients and oxygen in order to grow and divide [92], and thus without an adequate blood supply cancers might not grow [93]. Angiogenesis is the physiological process through which new blood vessels form from pre-existing vessels [94]. Cancers induce angiogenesis by secreting various growth factors such as vascular endothelial growth factor (VEGF) which is the major contributor to angiogenesis, increasing the number of capillaries in a given network [95]. Inhibition of cancer angiogenesis is increasing the death of the tumor tissue (necrosis) whereas the presence of tumor necrosis within primary tumors is associated with angiogenesis responses.
Furthermore, cancer cell motility, migration and invasion play fundamental roles in cancer metastasis [99]. Therefore, inhibiting either cancer cell motility, migration or invasion impede metastasis, which is the cause of over 90% of patient deaths [100].

EGCG has demonstrated potential efficacy in inhibiting angiogenesis, necrosis, motility, invasion, migration and metastasis markers in a variety of human cancers tested under preclinical model systems. In A549 lung cancer cells, EGCG was observed to inhibit angiogenesis and reduce xenograft tumor growth through inhibiting IGF-1 via suppressing HIF-1α and VEGF protein expression [101–104], upregulation of endostatin expression [102], inhibition of HPV-16 oncoprotein induced angiogenesis conferred by cancer cells via inhibition of HIF-1α protein expression and HIF-1α dependent expression of VEGF, IL-8, and CD31 and activation of Akt [104]. In addition, EGCG inhibits nicotine-induced migration, invasion through upregulation of HIF-1α, VEGF, COX-2, p-Akt and p-ERK [105]. Similarly, in lung NCI-H460 cancer cells, EGCG inhibits angiogenesis through inhibition of HIF-1α protein expression and HIF-1α dependent expression of VEGF, IL-8, and CD31 as well as activation of Akt [104]. EGCG also was able to inhibit cell motility in vitro wound healing assay in H1299 and Lu99 lung cancer cells [106]. In ovarian cancer, EGCG inhibited cell motility through suppression of Hsp90 chaperone system in SKOV3 cells [107]. On breast cancer, only 10 μM of EGCG was able to inhibit cell migration through downregulation of VEGF expression in Hs5787 breast [130]. In NPY39 breast cancer cells, EGCG inhibited branching colony growth and cell invasion through induction of estrogen receptor α expression via activating FOXO3a signaling [108]. EGCG inhibits cell migration and invasion through downregulation of VASP expression and Rac1 activity [109] in MCF-7 cancer cells. EGCG also inhibits cell motility and migration in MDA-MB-231 through inhibition of EGFR-induced MMP-9 via suppressing FAK and ERK signaling pathways [110]. In oral cancer, in SCC-9 cells, EGCG inhibited invasion, epithelial-mesenchymal transition, and tumor growth through downregulation of MMP-2, uPA, p-FAK, p-Src, snail-1 and vimentin [111]. EGCG inhibits HGF-induced cell growth and invasion through suppression of HGF/c-Met signaling pathway [112]. Repressing of functional invadopodia formation was done by EGCG to inhibit in vitro and in vivo invasion in HSC-3 and YD-10B oral cancer cells FAK/Src signaling [113]. In Hypopharyngeal FaDu and laryngeal SNU-899 and SNU-1066 cancer cells, EGCG Inhibited HGF-induced cell growth and invasion through suppression of HGF/c-Met signaling pathway [112]. In gastric cancer, EGCG inhibited xenograft angiogenesis and tumor growth in BGC-823 [40]. EGCG inhibited IL-6-induced angiogenesis in vitro and in vivo through inhibition of VEGF expression via suppressing Stat3 activity in AGS cells [114]. In SGC-7901 cancer cells, EGCG inhibited tumor growth and angiogenesis through reducing VEGF-induced endothelial cell proliferation, migration and tube formation [115]. In squamous cell carcinoma, EGCG inhibited HGF-induced cell growth and invasion through suppression of HGF/c-Met signaling pathway in SCC VII/SF cells while it inhibited xenograft tumor growth in vivo via rising apoptosis [112]. In hepatocellular carcinoma, in Hepa 1c1c7 cells, EGCG inhibited cell motility via suppression of Hsp90 chaperone system [107]. In cervical cancer, EGCG inhibited cell proliferation, invasion and migration in HeLa cells through downregulation of MMP-9 gene and upregulation of TIMP-1 gene [85]. In colorectal cancer, EGCG inhibited tumor growth in vitro in SW837 cells and in vivo and through activation of VEGF/VEGFR axis via suppressing the expression of HIF-1α and several major growth factors [116]. EGCG also inhibited migration and proliferation in SW620 cells in vitro through inactivation of PAR2-AP and factor VIIa and by the way inhibition of the ERK1_2 and NF-kB pathways [117]. Moreover, EGCG inhibits liver metastasis in vivo RKO colorectal cancer cells experiments and suppresses angiogenesis and induces apoptosis.
in liver metastasis [118], EGCG inhibited Met signaling which helps to attenuate tumor spread/metastasis, independent of H$_2$O$_2$-related mechanisms in HCT-116 and HT-29 colorectal cancer cells [119,120]. In bladder cancer, EGCG inhibited cell adhesion, migration and invasion in T-24 cells through downregulation of MMP-9 expression via blocking of NF-kB signaling pathway [121]. In esophageal TE-8 and SKGT-4 cancer cells, EGCG reduced cell viability and invasion in vitro through reduction of p-ERK1/2, c-Jun and COX-2, and activation of caspase-3 whereas it inhibits tumor growth in vivo through suppressing the expression of Ki67, p-ERK1/2 and COX-2 [32]. In prostate cancer, EGCG inhibited cell motility and invasion through inhibition of c-Met signaling via altering the structure or function of lipid rafts in DU-145 cells [122]. In addition, EGCG Inhibited tumor growth and angiogenesis in CWR22Rv1 cells but promoting apoptosis of the prostate cancer cells in vitro [123]. In BCap101 cancer cells, EGCG inhibited cell motility in vitro via suppression of Hsp90 molecular chaperone system which supports malignant phenotype [124]. EGCG-P is more stable and effective than EGCG enhancing the inhibition of the tumor growth, angiogenesis of CWR22Rv1 prostate cancer cells in vivo [123].

Anticancer effects of EGCG combinations

Induction of apoptosis

Several studies have stated that EGCG and its combinations have induced apoptosis in a variety of cancers. EGCG as a green tea polyphenol (GTP) or combined with different natural molecules have been employed to induce apoptosis in different cancers. The general idea is that combination of two or more agents could target more pathways and thus will be more effective to increase the stability of the agent and reduce toxicity to simultaneously exhibit higher therapeutic outcome. Various studies found that EGCG synergistically induced cancer cells apoptosis in vitro and in vivo through different apoptotic signaling, upregulation of pro-apoptotic proteins and inhibition of anti-apoptotic proteins when combined with other natural molecules, such as vitexin-2-O-xyloside and raphasatin [46], curcumin [125], N-acetylcycteine (NAC) [126], pterostilbene [36], tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [74], quercetin [33], whole green tea polyphenols (GTPs) [127], eicosapentaenoic acid-free fatty acid (EPA-FFA) and grape seed (GS) extract [128], 5-fluorouracil (5-FU) [37], sodium butyrate (NaB) [43] and [6]-Gingerol and tocotrienol-rich fraction (TRF) [30].

Combination of EGCG with curcumin induces apoptosis through upregulation of caspase-dependent apoptotic signaling pathways in MCF-7 breast cancer cells [125]. However, a mixture of EGCG, vitexin-2-O-xyloside and raphasatin was found to induce apoptosis via mitochondrial pathway in breast MDA-MB-231 and MCF-7 and colorectal Caco-2 and LoVo cancer cells [46]. In addition, NAC and EGCG interact to form EGCG-2-NAC adduct which induces cell culture apoptosis in CL-13 lung cancer cells [126]. Also, pterostilbene and EGCG combination induced apoptosis in both Panc-1 and MIA-Pa-Ca-2 pancreatic cancer cells [36] Adding TRAIL to EGCG increases synergistically apoptosis induction via cleavage of procaspase-3 in MIA-Pa-Ca-2 cells [74]. Studies observed that natural small molecules, such as quercetin, can increase the bioavailability of EGCG in rats and human [129] enhancing apoptosis

Fig. 4. Schematic drawing of the regulative actions of EGCG combined with other dietary and pharmaceutical agents. This cartoon is based on the available literature.
Table 2
Compounds have previously combined with EGCG.

| Molecular structure | Molecular Formula | MW (g/mol) | Cancers (cell lines) |
|---------------------|-------------------|------------|----------------------|
| [6]-Gingerol        | C_{17}H_{26}O_{4}  | 294.391    | Glioma (SW1783, LN18 and 1321N1) [30] |
| Arginine            | C_{6}H_{14}N_{4}O_{2} | 174.204    | Prostate (PC-3, LNCaP and DU-145) [44] and bladder (T-24) [137] cancers |
| Ascorbic acid       | C_{6}H_{8}O_{6} or HC_{6}H_{7}O_{6} | 176.124    |                      |
| Curcumin            | C_{21}H_{20}O_{6}  | 368.385    | Breast (MDA-MB-231 [31] and MCF-7 [125,146]), lung (A549 [45] and NCI-H460 [45]), prostate (PC-3) [33] and nsophageal (TE-8 and SKGT-4) [32] cancers |
| Green tea polyphenols (GTP) |                   |            |                      |
| Epicatechin         | C_{14}H_{14}O_{6} | 290.26     | Prostate (LNCaP) cancer [147] |
| Epicatechin-3-gallate | C_{22}H_{18}O_{10} | 442.37     |                      |
| Epigallocatechin    | C_{15}H_{10}O_{7}  | 306.27     |                      |
| Kaempferol          | C_{15}H_{10}O_{6}  | 286.23     |                      |
| Quercetin           | C_{15}H_{10}O_{7}  | 302.236    | Prostate (PC-3 [33] and LNCaP [33,147]) cancer |
| Myricetin           | C_{15}H_{10}O_{6}  | 318.2351   | Prostate (LNCaP) cancer [147] |

(continued on next page)
| Molecular structure               | Molecular Formula | MW (g/mol) | Cancers (cell lines)                              |
|----------------------------------|-------------------|------------|-------------------------------------------------|
| Theogallin                       | C_{14}H_{16}O_{10} | 344.27     |                                                 |
| Chlorogenic acid                 | C_{16}H_{18}O_{9}  | 354.31     |                                                 |
| Coumarylquinic acid              | C_{16}H_{18}O_{8}  | 338.312    |                                                 |
| GS                               | C_{31}H_{28}O_{12} | 592.553    | Colorectal (HCT-116 and SW480) cancer[128]     |
| Polyphenon E                     | C_{8}H_{10}N_{4}O_{2} | 194.194   | Lung cancer [148]                               |
| (+)-Gallocatechin                | C_{15}H_{14}O_{7}  | 306.27     |                                                 |
| EGC                              |                   |            |                                                 |
| (+-)-Catechin                    | C_{15}H_{14}O_{7}  | 290.271    |                                                 |
induced against cancer cells due to EGCG treatment, such as in LNCaP and PC-3 prostate cancer cells [33]. In vivo GTPs (including that contains EGCG) oral infusion resulted in significant apoptosis of cancer cells causing inhibition of prostate cancer development, progression, and metastasis [127]. A combination of EGCG, eicosapentaenoic acid-free fatty acid and grape seed extract [128] or a mixture of EGCG and Fluorouracil (5-FU) [37] induced apoptosis in both HCT-116 and SW480 colorectal cancer cells [37,128]. Also apoptosis through survivin downregulation has been noted when HCT-116, HT-29 and RKO colorectal cancer cells are treated with a combination of EGCG and NaB [43]. Finally, both EGCG and [6]-Gingerol or EGCG and TRF combinations both can induce apoptosis in 1321N1, LN18 and SW1783 glioma cells through activation of caspase-3 [30].

On the other hand, cancer stem cells (CSCs) have been identified in a number of solid tumors, including breast cancer, brain tumors, lung cancer, colon cancer, and melanoma [130]. CSCs have the capacity to self-renew, to give rise to progeny that are different from them, and to utilize common signaling pathways [130,131]. CSCs may be the source of all the tumor cells present in a malignant tumor, the reason for the resistance to the chemotherapeutic agent used to treat the malignant tumor, and the source of cells

Table 2 (continued)

| Molecular structure | Molecular Formula | MW (g/mol) | Cancers (cell lines) |
|---------------------|-------------------|------------|---------------------|
| Gallocatechin gallate | C_{22}H_{18}O_{11} | 458.375 | Pancreatic (PANC-1 and MIA-Pa-Ca-2) cancer [36] |
| ECG | | | |
| (-)-Catechin gallate | C_{22}H_{18}O_{10} | 442.376 | Prostate (PC-3) cancer [34] |
| EGC | | | |
| pterostilbene | C_{14}H_{16}O_{3} | 256.301 | Pancreatic (PANC-1 and MIA-Pa-Ca-2) cancer [36] |
| Sulforaphane | C_{6}H_{11}NOS_{2} | 177.28 | Prostate (PC-3) cancer [34] |
| Tocotrienol-rich fraction (TRF) | C_{28}H_{42}O_{2} | 410.642 | Glioma (1321N1, LN18 and SW1783) [30] |
| TRAIL | – | – | Pancreatic (MIA-Pa-Ca-2) cancer [74] |
| Cancers         | Cell lines               | EGCG Combination | Dose & IC_{50} | Biological effects                                                                 |
|-----------------|--------------------------|------------------|----------------|-----------------------------------------------------------------------------------|
| **Breast cancer** | MDA-MB-231               | EGCG             | 50 and 100 μM [149]; 50 and 80 μg/mL [73]; 20, 40 and 60 μM [150]; 10 and 20 μM [110]; 0.01–1000 μM [151]. | IC_{50}: 50 μM (24 h) [149], 15.7 μM [151]. | Inhibits cell proliferation and viability through suppression of Wnt signaling via inducing the HBP1 transcriptional repressor [149], epigenetic repression of hTERT [150] and inhibition of glucose uptake and metabolism [151]. Induces cell apoptosis through downregulation of pro-apoptotic signaling and downregulation of MMP-9 expression [79]. Inhibits cell invasion, motility and migration through inhibition of EGF-induced MMP-9 via suppressing FAK and ERK signaling pathways [110]. |
|                 |                          | pEGCG            | 20 μM [150]; 50 μmol/L [79]. | Induct cell proliferation via Epigenetic repression of hTERT [150]. In addition, it inhibits significantly tumor growth in vivo associated with increased proteasome inhibition and apoptosis induction in tumor tissues [79]. |
|                 |                          | EGCG + Curcumin  | E (20,25,35 and 40 μM) and/or C (2,3,4 and 6 μM) | \ | Inhibits cancer proliferation in vitro and in xenograft mouse models through inhibition of VEGFR-1, EGFR and AKT protein level [31]. |
|                 |                          | EGCG (E) + Vitexin-2-O-xyloside (X) + Raphasatin (G) | E (10,20,30,40,50 μg/mL) × (30,50,80, 100,120 μg/mL) and/or G (5,10,15,30,50 μg/mL). | IC_{50}: E (135 ± 16), X (158 ± 13), G (36 ± 5) μg/mL. | Mixture activates ROS mediated mitochondrial pathway causing G0/G1 cell cycle arrest and induces apoptosis [46]. |
|                 |                          | EGCG-Ptx-PLGA-Casein-NPs | – | – | |
|                 |                          | EGCG-LbL-PSS/PAH-NPs | 1 or 5 μM [152] | – | Induce apoptosis, inhibit NF-kB activation and downregulate the key genes associated with angiogenesis, tumor metastasis and survival [141]. |
|                 |                          | EGCG             | 10, 20, 30, 40 and 50 [73]; 10, 25, 50 and 100 [109]; 1 and 10 μM [153]; 20, 40 and 60 [150]; 0.01–1000 μM [151]; 10, 20 and 40 μM [154]; 0.1, 1, 10, 50 and 100 μM [146]. | IC_{50}: 50 μg/mL [73,109]; 44.1 μM [151] 40 μM [154]; 19–20 μM [146]. | Inhibit HGF-induced c-Met signaling after prolonged pre-incubation [13,152]. |
|                 |                          | pEGCG            | 20 μM [150] | – | Inhibit cell proliferation via epigenetic repression of hTERT [150]. |
|                 |                          | EGCG + Curcumin  | E (2, 4, 10, 20, 40, 100) μM + C 20 μM | – | Induce growth inhibition and apoptosis through upregulation of caspase-dependent apoptotic signaling pathways and inhibition of P-glycoprotein pump function [125]. |
|                 |                          | EGCG (E) + Vitexin-2-O-xyloside (X) + Raphasatin (G) | E (10,20,30,40,50 μg/mL), X (30,50,80, 100,120 μg/mL) and G (5,10,15,30,50 μg/mL). | IC_{50}: E (135 ± 16), X (158 ± 13), G (36 ± 5) μg/mL. | Mixture activates ROS mediated mitochondrial pathway causing G0/G1 cell cycle arrest and induces apoptosis [46]. |
| **Hs578T**      | T47D                     | EGCG             | 10 μM | – | Inhibits cell proliferation and migration trough downregulation of VEGF expression [155]. |
| **NF639**       | T47D                     | EGCG             | 10, 20 and 40 μM. | IC_{50}: 40 μM | Inhibits cell proliferation trough epigenetic downregulation of ER-α via p38MAPK/CK2 activation [154]. |
|                 | T47D                     | EGCG             | 20, 40, 60 and 80 μg/mL [156]; 40 μg/mL [108] | – | Inhibits Her-2/Neu signaling, proliferation, and transformed phenotype of the Cancer Cells [156]. |
| **4 T1**        | T47D                     | EGCG             | 10 μg/kg, IP injection on day 7, 9 and 11 | – | Suppresses tumor growth in vivo by inhibiting tumor-associated macrophage infiltration and M2 polarization [157]. |
| **ALDH1+ in SUM-149 and SUM-190 stem cells** | T47D                     | EGCG             | 20, 40, 80 and 120 μg/mL | – | Inhibits growth of cancer stem cells in vitro and in vivo. Inhibits spheroid formation and induces apoptosis [133]. |
| **CD44+/CD24- in MDA-MB-231 and MDA-MB-436 stem cells** | T47D                     | EGCG             | 20, 30 and 40 μM | – | Inhibits tumorsphere formation and reduces cancer stem cell population through downregulation of estrogen receptor-α36, EGFR, p-ERK1/2 and p-AKT [158]. |
| Lung Cancer | A549  | EGCG  | 40–300 μM, IC_{50}: 265 ± 7.1 μM (24 h) in vitro and 40 mg/kg/week by IP injection into BALB/c nude female mice for 33 days [101]. 50 and 100 μM in vitro and 0.05% in drinking water into BALB/c nude male mice for 21 days [102]. 1, 5, 10, 20 and 40 μM [159]. 10, 25, 50 and 100 [104,105]. 10–40 μM [86]. 80 μM [160]. 25 and 100 [161]. 100 μM into flanks of nude mice [103–105]. 5,10,25 and 50 [162]. | Induces cell apoptosis through inhibition of FASN activity and EGFR signaling pathway [101]. Reduces xenograft tumor growth and angiogenesis in vivo [101,102] through inhibiting of oncogene and IGF-1 via suppressing HIF-1α and VEGF expression [103,104]. Inhibits cell proliferation through upregulation of endostatin expression and suppression of VEGF expression [102] and suppression of the expression of the cell death-inhibiting gene, Bel-7 [161]. Inhibits cell growth through induction of G0/G1 cell cycle arrest via inhibiting EGFR/cyclin D1 signaling [86] and upregulation of miR-210 expression via stabilizing HIF-1α [162]. Inhibits the anchorage-independent growth of cancer cells, induces p53 accumulation and upregulates its target genes, promotes the stability of p53 and MDM2, promotes nuclear localization and activity of p53, inhibits prosaposin degradation-dependent p53 ubiquitination and inhibits the interaction of p53 and MDM2 [159]. Inhibits HPV-16 oncoprotein induced angiogenesis conferred by cancer cells through the inhibition of HIF-1α protein expression and HIF-1α dependent expression of VEGF, IL-8, and CD31 as well as activation of Akt [104]. Inhibits cancer chemosensitization variants through downregulation of Axln and Tyro 3 expression [160]. Inhibits nicotine-induced migration, invasion and upregulation of HIF-1α, VEGF, COX-2, p-Akt and p-ERK [105]. |  |
| --- | --- | --- | --- | --- |
| CL13  | EGCG  | 5,10,25 and 50 | EGCG + Curcumin 10,20,40 μM EGCG and/or the same concentrations for curcumin in vitro while fourteen 3 to 4-week old female BALB/c nude mice were i.p. implanted with 5 × 106 A549 cells. At the third day after the A549 cells injected, the mice were randomized into two groups (7 mice/group) and treated with control (NS, 100 mL/kg) or EGCG and curcumin (20 mg/kg, respectively) [45]. | Suppresses cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1α [162]. EGCG and NAC interact to form EGCG-2'-NAC adduct which induces cell culture apoptosis [126]. |
| H1299  | EGCG  | (0–100) μM of EGCG in the presence or absence of 0–2 mM NAC. | EGCG + N-acetylcysteine (NAC) 10,20,30,40 and 50 μM in vitro, 0.1, 0.3 and 0.5% in diets and 30 mg/kg/d by IP injection into male NCr nu/nu mice for 45 days. IC_{50}: 20 μM in vitro and 0.15 μM in vivo [163]; 5,10,25 and 50 [162]. | Inhibits cancer growth in vivo and in vitro and induces ROS and cell apoptosis [163]. Suppresses cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1α [162]. |
| H1650  | EGCG  | 1.5,10,20 and 40 μM [159]. 10–40 μM [86]. 80 μM [160]. 5,10,25 and 50 | Inhibits the anchorage-independent growth of cancer cells, induces p53 accumulation and upregulates its target genes, promotes the stability of p53 and MDM2, promotes nuclear localization and activity of p53, inhibits prosaposin degradation-dependent p53 ubiquitination and inhibits the interaction of p53 and MDM2 [159]. Inhibits cell growth through induction of G0/G1 cell cycle arrest via inhibiting EGFR/cyclin D1 signaling [86]. Inhibits cancer proliferation including their chemoresistant variants through downregulation of Axln and Tyro 3 expression [160]. Suppresses cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1α [162]. |  |
| H1299  | EGCG  | 1.5,10,20 and 40 μM [159]. 10–40 μM | Inhibits the anchorage-independent growth of cancer cells, induces p53 accumulation and upregulates its target genes, promotes the stability of p53 and MDM2, promotes nuclear localization and activity of p53, inhibits prosaposin degradation-dependent p53 ubiquitination and inhibits the interaction of p53 and MDM2 [159]. Inhibits cell growth through induction of G0/G1 cell cycle arrest via inhibiting EGFR/cyclin D1 signaling [86]. |  |
| Lu99  | EGCG  | 5,10,50 and 100 μM | Reduces cell motility in vitro wound healing assay. Increases Young’s modulus of H1299 from 1.24 to 2.25 showing a 2-fold increase in cell stiffness, i.e. rigid elasticity of cell membrane. Furthermore, inhibits high expression of vimentin and Slug in the cells at a leading edge of scratch. Induces inhibition of EMT phenotypes by alteration of membrane organization [106]. |  |

(continued on next page)
Table 3 (continued)

| Cancers                      | Cell lines               | EGCG Combination | Dose & IC50                                                                 | Biological effects                                                                 |
|------------------------------|--------------------------|------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Pancreatic cancer            | AsPC-1                   | EGCG             | 5–80 μM [48]                                                               | Induces apoptosis through cell cycle via G1 cell cycle arrest, regulation of cyclin D1, cdk4, cdk6, p21 and p27. Activation of ROS-mediated, p53-dependent apoptosis signaling, induction of Ras/Raf-1/ERK1/2 signaling, induction of MEKK1, JNK1/2 and p38 MAPK activities [48]. |
|                              | Hs 766 T                 | EGCG             | 5–80 μM [48]                                                               | The combination have additive, antiproliferative effects in vitro altering the apoptotic mechanisms by modulation at different points in the mechanism as well as the cell cycle arrest effect [36]. |
|                              | Panc-1                   | EGCG             | 20, 30, and 40 μM EGCG with/without 30 μM Pterostilbene                    | Induces apoptosis through cell cycle via G1 cell cycle arrest, regulation of cyclin D1, cdk4, cdk6, p21 and p27. Activation of ROS-mediated, p53-independent apoptosis signaling, induction of Ras/Raf-1/ERK1/2 signaling, induction of MEKK1, JNK1/2 and p38 MAPK activities [48]. |
|                              | MIA-Pa-Ca-2              | EGCG             | 10, 100, and 1000 μM, IC50 below 50 μM [165]; 5–80 μM [48]                 | Inhibits cell proliferation and induces apoptosis through inhibition of cell cycle and DNA synthesis inducting NDA damage [166]. Downregulates AQP5, nuclear p65 and IκBα expressions [167]. |
|                              |                          | EGCG + TRAIL     | 50 μg/ml E+5 ng/ml T                                                       | Provides antitumor immunity through inhibition of indoleamide 2,3-dioxygenase (IDO) expression via blocking the IFN-γ-induced JAK-PKC-STAT1 signaling pathway [168]. |
| Ovarian cancer               | SKOV3                    | EGCG             | 20, 30, 40, and 50 μg/mL [166]; 20, 40, 60, 100, and 120 μg/mL [167]; 100 μM [107] | Inhibits cell motility via suppression of Hsp90 chaperone system [107]. |
| Oral cancer                  | SAS                      | EGCG             | 20 and 40 μM [168]                                                         | Provides antitumor immunity through inhibition of indoleamide 2,3-dioxygenase (IDO) expression via blocking the IFN-γ-induced JAK-PKC-STAT1 signaling pathway [168]. |
|                              | Cal-27                   | EGCG             | 5,10,15, and 20 μM in vitro; 10 and 20 mg/day/kg by or by oral gavage into the right front axilla of BALB/c nude mice | Inhibits invasion, epithelial-mesenchymal transition, and tumor growth through downregulation of MMP-2, uPA, p-FAK, p-Src, snail-1 and vimentin [111]. |
|                              | Ca-922                   | EGCG             | 20 and 40 μM [168]; 10, 20, 50, 100, and 200 μM [169]                      | Provides antitumor immunity through inhibition of indoleamide 2,3-dioxygenase (IDO) expression via blocking the IFN-γ-induced JAK-PKC-STAT1 signaling pathway [168]. |
|                              | SCC-9                    | EGCG             | 5,10,20,40,80,100,150 and 200 μM                                           | Provides antitumor immunity through inhibition of indoleamide 2,3-dioxygenase (IDO) expression via blocking the IFN-γ-induced JAK-PKC-STAT1 signaling pathway [168]. |
|                              | KB                       | EGCG             | 5,10,20,40,80,100,150 and 200 μM                                           | Provides antitumor immunity through inhibition of indoleamide 2,3-dioxygenase (IDO) expression via blocking the IFN-γ-induced JAK-PKC-STAT1 signaling pathway [168]. |
|                              | HSC-3                    | EGCG             | 20 and 40 μM [168]; 10,25,50 and 100 μM [113]                            | Provides antitumor immunity through inhibition of indoleamide 2,3-dioxygenase (IDO) expression via blocking the IFN-γ-induced JAK-PKC-STAT1 signaling pathway [168]. |
|                              | YD-10B                   | EGCG             | 10,25,50 and 100 μM in vitro; 20 mg/d/kg IP injection into the tongue of male BALB/c athymic nude mice every other day for 4 weeks | Inhibits cancer invasion in vitro and in vivo via repressing functional invadopodia formation [113]. |
| Hypopharyngeal cancer        | FaDu                     | EGCG             | 5,10,20,40,80,100,150 and 200 μM                                           | Inhibits HGF-induced cell growth and invasion through suppression of HGF/c-Met signaling pathway [112]. |
| Laryngeal cancer             | SNU-899 (Oct4high/Nanoghigh/β-cateninhigh/ABCG2high/MPR-1high/MDR-1high) in TW01 CSCs | EGCG             | 5,10,20,40,80,100,150 and 200 μM                                           | Inhibits HGF-induced cell growth and invasion through suppression of HGF/c-Met signaling pathway [112]. |
| Nasopharyngeal cancer        | SNU-1066 (Oct4high/Nanoghigh/β-cateninhigh/ABCG2high/MPR-1high/MDR-1high) in TW06 CSCs | EGCG + Cisplatin (20 and 40 μM) E and/or (0.01, 0.1, 1 and 10 μg/mL) C | Mixture inhibits spheroid formation and cell viability as well as EGCC enhances chemo-sensitivity of cisplatin in vitro through downregulation of Oct4, β-Catenin, Nanog, ABCG2, MRP-1, MDR-1, p-STAT3, Bcl-2, Survivin and c-Myc [170]. |
EGCG increases chemo-sensitivity of cisplatin in vivo [138].

Inhibits nasopharyngeal cancer stem cell self-renewal and migration and reverses the epithelial-mesenchymal transition via NF-κB p65 inactivation [138].

CD44+ in CNE2 CSCs

EGCG 20 μM + Cisplatin (10 μM) were injected subcutaneously into the flanks of nude mice and allowed to grow for 8 weeks

Inhibits nasopharyngeal cancer stem cell self-renewal and migration and reverses the epithelial-mesenchymal transition via NF-κB p65 inactivation [138].

Inhibits xenograft angiogenesis and tumor growth [40].

Inhibits IL-6-induced angiogenesis in vitro and in vivo through inhibition of VEGF expression via suppressing Stat3 activity [114].

Inhibits cell proliferation and induces cell apoptosis through downregulation of Id1 expression [171].

Inhibits cell proliferation through downregulation of DEAD-box RNA helicase p68 [172].

Induces cell apoptosis through inhibition of survivin expression downstream of p73 [78].

Inhibit cell motility via suppression of Hsp90 chaperone system [107].

Induces non-apoptotic cell death via ROS-mediated lysosomal membrane permeabilization [173].

Induces cell apoptosis through upregulation of caspase-9a expression [47].

Induce sphere formation through inhibition of CD133, Nanog, ABCC1, ABCG2, Nek2 and p-Akt [174].

Induces cell apoptosis within over 5-fold dose advantages compared to EGCG alone in in-vitro system [142].

Combination significantly decreased the viability of cells, compared with EGCG or 5-FU-treated cells [174].

Combination inhibits cell proliferation and induction of cell apoptosis in vitro by increasing the intracellular concentration of EGCG and decreasing EGCG methylation [33].

Reduction of cell viability via inhibition of AP-1 activation [34].

Induction of cell cycle arrest at both S and G2/M phases via upregulating p21 protein level [135].

Induction of cell proliferation and invasion through reducing VEGF-induced endothelial cell proliferation, migration and tube formation [115].

Inhibit tumor growth and angiogenesis through reducing VEGF-induced endothelial cell proliferation, migration and tube formation [115].

Inhibit cell motility via suppression of Hsp90 chaperone system [107].

Induces non-apoptotic cell death via ROS-mediated lysosomal membrane permeabilization [173].

Induces cell apoptosis through upregulation of caspase-9a expression [47].

Induces cell apoptosis within over 5-fold dose advantages compared to EGCG alone in in-vitro system [142].

(continued on next page)
| Cancers | Cell lines | EGCG Combination | Dose & IC50 | Biological effects |
|---------|------------|------------------|-------------|-------------------|
| NPs enhance the bioavailability and limited unwanted toxicity of EGCG within 10-fold dose advantage [13]. In addition, induce apoptosis within remarkably significant increase in pro-apoptotic Bax with a concomitant decrease in anti-apoptotic Bcl-2, increase in PARP cleavage and marked induction of p21 and p27 [20]. In vivo, NPs enhance the anti-proliferative activity compared to the free EGCG modulating apoptosis and cell-cycle. In vivo, NPs enhance the bioavailability and limited unwanted toxicity [49]. Combination enhances the inhibition of metastatic tumor growth [41]. |
| PC-3ML | EGCG + Doxorubicin | 30 and 60 µM E+ D in vitro; 0.14–57 mg/kge and/or 2 mol/L-0.07 mg/kg D into immunodefiency mice | | Inhibits growth and spheroid formation, induces apoptosis, inhibits EMT, inhibits migration and invasion and downregulates Casp3/7, Bcl-2, Survivin, XIAP, Vimentin, Slug, Snail and nuclear β-Catenin [132]. |
| (CD44+/CD133+ in PC-3) CSC | EGCG | 30 and 60 µM | | Modulates cell growth, by affecting mitogenesis as well as inducing apoptosis, in cell-type-specific manner which may be mediated by WAF1/p21-caused G0/G1-phase cell-cycle arrest, irrespective of the androgen association or p53 status of the cells. Inhibits cell proliferation through inhibition of PKC-α inhibition [177], prostate specific antigen (PSA) expression, AR transcriptional activity, growth of relapsing R1Ad tumors and tumor derived serum PSA in vivo [178]. In vitro and in vivo inhibition of testosterone-mediated induction of ornithine decarboxylase1 [147]. Quercetin enhances the anti-proliferative effects of EGCG and induction of cell apoptosis in vitro through increasing the intracellular concentration of EGCG and decreasing EGCG methylation [33]. Combination inhibits cell proliferation and invasion through downregulation of MMP-2 and MMP-9 expressions [44]. |
| LNCaP | EGCG | 12 µM [177]; 20,40 and 80 µM [178]; 10, 20, 40, and 80 µg/mL [87] | | Inhibits growth and spheroid formation, induces apoptosis, inhibits EMT, inhibits migration and invasion and downregulates Casp3/7, Bcl-2, Survivin, XIAP, Vimentin, Slug, Snail and nuclear β-Catenin [132]. |
| Green tea polyphenols (GTP) | EGCG + Quercetin | 80 µM EGCG and/or 10 and 20 µM Quercetin 50 microg/mL; 500 µg/mL of the mixture | | Inhibits cell motility and invasion through inhibition of c-Met signaling via altering the structure or function of lipid rafts [122]. |
| (CD44+/CD133+ in LNCaP) CSCs | EGCG | 30 and 60 µM | | Inhibits growth and spheroid formation, induces apoptosis, inhibits EMT, inhibits migration and invasion and downregulates Casp3/7, Bcl-2, Survivin, XIAP, Vimentin, Slug, Snail and nuclear β-Catenin [132]. |
| DU-145 | EGCG | 5 µM; 10, 20, 40, and 80 µg/mL [87] | | Modulates cell growth, by affecting mitogenesis as well as inducing apoptosis, in cell-type-specific manner which may be mediated by WAF1/p21-caused G0/G1-phase cell-cycle arrest, irrespective of the androgen association or p53 status of the cells. Inhibits cell motility and invasion through inhibition of c-Met signaling via altering the structure or function of lipid rafts [122]. Combination inhibits cell proliferation and invasion through downregulation of MMP-2 and MMP-9 expressions [44]. |
| CWR22R | EGCG | 50 mg/kg/d IP injection into nude mice for 20 days. | | Inhibits tumor growth and angiogenesis while promoting apoptosis of the prostate cancer cells in vivo [123]. EGCG-P is more stable and effective than EGCG enhancing the inhibition of the tumor growth, angiogenesis and induces apoptosis of the prostate cancer cells in vivo [123]. |
| BCaPT10 | EGCG | 86.7 mg/kg/d IP injection into nude mice for 20 days. 2–200 µM in vitro; 0.06% in water into male athymic mice for 1 week before xenograft surgery | | Inhibits cell motility in vitro via suppression of Hsp90 molecular chaperone system which supports malignant phenotype [124]. |
| BCaPM-T10 | EGCG | 0.06% in water into male athymic mice for 1 week before xenograft surgery | | Inhibits a molecular chaperone supportive of the malignant phenotype [124]. |
| 22Rv1 | EGCG-CS-NPs | 3 and 6 mg/kg by oral administration into athymic nude mice for 25 days | | Inhibit AR-positive 22Rv1 tumor xenograft growth and secreted prostate-specific antigen levels compared with EGCG and control groups. Significant induction of poly (ADP-ribose) polymerases cleavage, increase in the protein expression of Bax with concomitant decrease in Bcl-2, activation of caspases and reduction in Ki-67 and proliferating cell nuclear antigen [163]. Inhibits cell proliferation and induces apoptosis through downregulation of AR, IGF-1, IGF-1R, p-ERK 1/2, COX-2, and iNOS [179]. |
| – | EGCG | Five-week-old male TRAMP offspring were fed AIN-76A diet and 0.06% EGCG in tap water for 28 weeks | | Inhibit AR-positive 22Rv1 tumor xenograft growth and secreted prostate-specific antigen levels compared with EGCG and control groups. Significant induction of poly (ADP-ribose) polymerases cleavage, increase in the protein expression of Bax with concomitant decrease in Bcl-2, activation of caspases and reduction in Ki-67 and proliferating cell nuclear antigen [163]. Inhibits cell proliferation and induces apoptosis through downregulation of AR, IGF-1, IGF-1R, p-ERK 1/2, COX-2, and iNOS [179]. |
Melanoma

Mel 928
EGCG-CS-NPs
0.5, 1, 2, 4.0 and 8.0 μM in vitro; IC50: 7 μM (48 h); 100 μM/mice; 120 μL treatment volume into Athymic (nu/nu) male nude mice.

Leukemia

CEM
(MSN@EGCG)-NPs
0.4, 0.8, 1.2 and 1.6 μM in vitro and 100; NPS are i.v. injected into female Balb/c mice

Colorectal cancer

HCT-116
EGCG
10, 25, 50 and 100 μM [88]; 10,20,30,40,50,60,70,80,90 and 100 μM [89]; IC50: 47.9 μM [88]; 100 μM (24 h) and 50 μM (48 h) [85].

Cervical cancer

HeLa
EGCG
100, 25, 50 and 100 μM. IC50: 27.3 μM (24 h) [84].

CatiSki
EGCG
0.05, 0.1, 0.5, 1, 5 and 10 μM [119]; 0.1, 0.5, 1, 5 and 10 μM [120]; 1, 10 and 50 μM [89]; 50 and 100 μM [181]; 12.5, 25, 50 and 100 μM [118].

EGCG +Panaxadiol
E (0.10, 20 and 30 μM) and/or P (0,10 and 20 μM)

EGCG +EPA-FFA + GS
EGCG (0–175 μM) + EPA-FFA (0–150 μM) + GS extract (0–15 μM) for 24 h

EGCG +5-FU
5-FU (0.05 μg) and EGCG (25 μmol) [174]; 25–400 μM of EGCG and/or 2.5–40 μM 5-FU [37].

EGCG +NaB
10 μM E (+1,2,3,4,5 and 6 mM) N. IC50: 10 μM E + 5 mM N

CD133 and NANOG in HCT-116 stem cells

CD44, CD133 and ALDH1 in HCT-116 stem cells

HCT-8

EGCG
10,20 and 35 μg/mL [182]

Caco-2

EGCG
1, 5 and 10 μM [183]; 1, 10 and 50 μM [89]

EGCG (E) + Vitexin-2-O-xyloside (X) + Raphasatin (G)
E (10,20,30,40,50 μg/mL), X (30,50,80,100,120 μg/mL) and G (5,10,15,30,50 μg/mL);
IC50: E (135 ± 16), X (158 ± 13), G (36 ± 5) μg/mL

HT-29

EGCG-CS-CPP-NPs
0.063, 0.125 and 0.250 mg/mL

EGCG
0.1, 0.5, 1, 5 and 10 μM [120]; 1, 10 and 50 μM [89]; 10,20 and 35 μg/mL [182]; 5, 10 and 20 μg/kg/d oral gavage to male BALB nude mice for 28 days [185] or/14 days [182].

EGCG +NaB
10 μM E (+1,2,3,4,5 and 6 mM) N. IC50: 10 μM E + 5 mM N

In vivo GTP oral infusion resulted in almost complete inhibition of distant site metastases. Furthermore, GTP consumption caused significant apoptosis of cancer cells causing inhibition of prostate cancer development, progression, and metastasis [127]. Induce apoptosis and cell cycle inhibition along with the growth of Mel 928 tumor xenograft. Inhibited proliferation (Ki-67 and PCNA) and induced apoptosis (Bax, PARP) in tumors harvested from the treated mice within 8-fold dose advantage of nanoformulation over native EGCG [144].

In inhibit viability and proliferation in vitro and in vivo within a highly biocompatible and biodegradable EGCG-coated MSN nanoparticles [180].

Cell growth inhibition trough gene expression regulation and induction of cell cycle arrest [88]. Inhibit cell proliferation, invasion and migration, and induce cell apoptosis through G1 cell cycle arrest and DNA damage, downregulation of MMP-9 gene and upregulation of TIMP-1 gene [85].

Combination completely inhibited the mTOR signaling. Moreover, the treatment led to changes of protein translation of ribosomal proteins, c-Myc and cyclin D1. In addition, combination reduces clonal capability of cells, with block of cell cycle in G0/G1 and induction of apoptosis [128]. Combination significantly decreased the viability of cells, compared with EGCG or 5-FU-treated cells [174] like the EGCG enhances 5-FU sensitivity and induces apoptosis in 5-FU resistant cancer cells [37].

The combination treatment induces apoptosis and G2/M cell cycle arrest through decrease in HDAC1, DNMT1, survivin and HDAC activity [43].

Induc apoptosis and affects cell cycle of cancer cells via inhibiting of HDAC1, Nanot2, survivin and HDAC activity [43].

Inhibit sphere formation through inhibition of CD133, Nanog, ARCC1, ABCG2, Nek2, and p-Akt [174].

Induces apoptosis and cell cycle arrest, attenuate spheroid formation and enhance chemosensitivity of 5-FU in vivo [37].

Induces cell growth inhibition trough gene expression regulation and induction of cell cycle arrest [88].

Induces cell growth inhibition as EGCG and 67LR at a physiological concentration can activate myosin phosphatase by reducing MPP51 phosphorylation [183] or through cyclin D1 degradation and p21 transcriptional activation via ERK, IKK and PI3K signaling pathway [89].

Mixture activates ROS mediated mitochondrial pathway causing G0/G1 cell cycle arrest and induces apoptosis [46].

Manipulates enhance stability, penetration and transportation of EGCG through cancer cells [184]. Inhibits Met signaling and helps to attenuate tumor spread/metastasis, independent of H2O2-related mechanisms [120]. Suppresses cancer cells growth through cyclin D1 degradation and p21 transcriptional activation via ERK, IKK and PI3K signaling pathway [89].

The combination treatment induces apoptosis and G2/M cell cycle arrest through decrease in HDAC1, DNMT1, survivin and HDAC activity [43].

(continued on next page)
| Cancers        | Cell lines | EGCG Combination | Dose & IC50 | Biological effects                                                                                                                                                                                                                                                                                                                                 |
|----------------|------------|------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SW837          |            | EGCG             | 25 µg/mL *in vitro*; 0.01% and 0.1% in drinking water to BALB/c nude mice for 35 days [116]; 10,50 and 100 µM [186]. | Inhibits tumor growth *in vivo* and *in vitro* through activation of VEGF/VEGFR axis via suppressing the expression of HIF-1α and several major growth factors [116]. Provides antitumor immunotherapy through inhibiting the expression and function of indoleamine 2,3-dioxygenase via suppression of STAT1 activation [186]. Suppresses cancer cells growth through cyclin D1 degradation and p21 transcriptional activation via ERK, IKK and PI3K signaling pathway [89]. Inhibits proliferation *in vitro* and *in vivo* and induces apoptosis and affects the cell cycle of cancer cells via inhibiting of HES1 and Notch2 expressions [182]. EGCG enhances 5-FU sensitivity and induces apoptosis in 5-FU resistant cancer cells [37]. |
| SW480          |            | EGCG + Panaxadiol| 1, 10 and 50 µM [89]; 10,20 and 35 µg/mL [182]. | Inhibit cell proliferation and induce cell cycle arrest [35]. Inhibits cell proliferation and induces cell cycle arrest [89]. Inhibits cell proliferation and migration *in vitro* through inactivation of PAR2-AP and factor VIIa and by the way inhibition of the ERK1/2 and NF-κB pathways [117]. Inhibits proliferation in *in vitro* and *in vivo* and induces apoptosis and affects the cell cycle of cancer cells via inhibition of HES1 and Notch2 expressions [182]. EGCG + [6]-Gingerol 50 g/mL and/or 2.5–40 µM 5-FU [37]. Combination completely inhibits the mTOR signaling and lead to changes in protein translation of ribosomal proteins, c-Myc and cyclin D1 and reduces clonal capability of cells, with block of cell cycle in G0/G1 and induction of apoptosis [128]. EGCG inhibits cell proliferation and induces apoptosis through activation of caspase-3 [30]. U251 |
| Cancer Type                  | Cell Line | EGCG Concentration | Effect                                                                                      |
|-----------------------------|-----------|--------------------|---------------------------------------------------------------------------------------------|
| Skin cancer                 | A431      | 5, 10, 20, 40, and 80 μg/mL [90]; 100–200 μM [91]; 10, 20, 40, and 60 μg/mL [188] | Inhibits cell growth, viability and induces cell apoptosis [90,91] through inhibition of EGFR signaling [91], inhibition of pRB-E2F/DP pathway [90], inducing cell cycle arrest [90,91], inhibition of Cip1/p21 but no change in Kip1/27, CDK2, and cyclin D1 and a decrease in CDK4 only at low doses [91] and inactivation of β-catenin signaling [188]. |
| SCC-13                      | EGCG      | 10,20,40 and 60 μg/mL [188]; 10,20,40,60 and 100 μM [189] | Reduces cell viability [188], induces cell apoptosis [188,189] and inhibits cell growth [189] through inactivation of β-catenin signaling [188] and influencing PcG-mediated epigenetic regulation of cell cycle-related genes [189]. |
| Esophageal cancer           | TE-8      | 200 μL of a 5% solution | Prevent the adverse effects of UV radiation in humans [190]. |
|                             | SKGT-4    | 40 μM in vitro | Reduces cell viability [188], induces cell apoptosis [188,189] and inhibits cell growth [189] through inactivation of β-catenin signaling [188] and influencing PcG-mediated epigenetic regulation of cell cycle-related genes [189]. |
| Adrenal cancer              | NCI-H295  | 10, 20, 30 and 40 μM in vitro; IC_{50}: 20.34 μM (48 h) | Induces cell apoptosis through activation of caspase-dependent, caspase-independent, the mitochondrial, death receptor and endoplasmic reticulum stress apoptotic signaling pathways. EGCG also downregulate the expression of anti-apoptotic proteins, including Bcl-2, Bcl-XL, and XIAP. It upregulate the expression of pro-apoptotic proteins, including Apaf-1, BAD and BAX. It regulate molecular chaperones, such as 70 kDa heat shock protein (HSP70), HSP90 and GRP78 [76]. |
| Bladder cancer              | T-24      | 10, 20, 40, 80 μg/mL | Mixture inhibits critical steps of cancer development and spread, such as MMP-2 and -9 secretions and invasion [137]. |
| Pheochromocytoma            | PC-12     | 15 mg/kg IP injection into male BALB/c nude mice every other day for 15 days | Inhibits tumor growth and induces cancer cell apoptosis via acetylation of amyloid precursor protein [77]. |
| Neuroblastoma               | (Nanog{\text{hi}}/Oct4{\text{hi}}/ATP7A{\text{lo}}/DKK2{\text{lo}}) in BE(2)-C CSCs | 1,10,50 and 100 μM | Inhibits the development of TICs in BE(2)-C cells as well as inhibits sphere formation and induces apoptosis [134]. |
| Ehrlich’s ascites carcinoma  | EAC       | E (20 mg/kg b.wt., orally through gavage) + HDHA-DOX-NPs (1.5 mg/kg b.wt.) intravenously into Swiss albino mice. | EGCG enhances the anticaner activities of HDHA-NPs significantly increasing the mean survival time of the animals and inducing apoptosis [145]. |
| Head and neck squamous carcinoma (HNSC) | K3, K4, K5 | EGCG + Cisplatin 5,10,20 and 50 μM E and/or 5,10 and 20 μM C | Inhibit sphere formation and CD44+ cell population; enhances chemosensitivity of cisplatin in vitro and in vivo through downregulation of Oct4, Sox2, ABC2, ABCG2 and Notch1 [39]. |
that give rise to distant metastases [130]. Recently, studies found that EGCG can induce apoptosis to inhibit CSCs in vitro and in vivo. Besides, its effect of spheroid formation inhibition in CSCs, it induces apoptosis, and enhances chemo-sensitivity of chemotherapeutics in CSCs, for instance, EGCG induces apoptosis through downregulating Casp3/7, Bcl-2, survivin and XIAP in PC-3 and LNCaP prostate CSCs [132]. In addition, EGCG treatment induced apoptosis in the breast SUM-149 and SUM-190 CSCs [133], colon HCT-116 CSCs [37] and neuroblastoma BE(2)-C CSCs [134], and enhance the chemosensitivity of 5-FU in vivo [37].

Modulation of cellular proliferation

On the other hand, EGCG and curcumin combination inhibits cell proliferation and growth in vitro and in vivo in lung A549 and NCI-H460 cancer cells through induction of cell cycle arrest at G1 and S/G2 phases via downregulating cyclin D1 and cyclin B1 [45] while same combination induces cell cycle arrest at both S and G2/M phases via upregulating p21 protein level in PC-3 prostate cancer cells [135]. EGCG, vitexin-2-O-xyloside and raphasatin mixture induces G0/G1 cell cycle arrest in MDA-MB-231 and MCF-7 breast, Caco-2 and LoVo colorectal cancer cells [46]. EGCG and pterostilbene combination has antiproliferative effects in vitro as a cell cycle arrest induction in pancreatic PANC-1 and Mia-PaCa-2 cancer cells [36]. Similarly, EGCG and panaxadiol mixture inhibit cell proliferation and induce cell cycle arrest in both HCT-116 and SW480 colorectal cancer cells [35]. EGCG, EPA-FFA and GS combination blocks cell cycle in G0/G1 in both HCT-116 and SW480 colorectal cancer cells [132]. EGCG and NaB combination treatment induces G2/M cell cycle arrest through decreasing survivin in HCT-116, HT-29 and RKO colorectal cancer cells [43]. Furthermore, EGCG inhibit cell proliferation via induction of cell cycle arrest and attenuate spheroid formation in colorectal HCT-116 CSCs [37].

Inhibition of angiogenesis and related mechanisms

EGCG combinations has also been observed to inhibit angiogenesis, necrosis, motility, invasion, migration and metastasis in experimental cancer systems. In vivo GTP oral infusion resulted

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**Fig. 5.** Schematic drawing of the regulative actions of EGCG combined with nanoparticles. This carton is based on the available literature.
in almost complete inhibition of distant site metastases in prostate cancer. Furthermore, GTP consumption caused significant apopto-
sis of cancer cells causing inhibition of prostate cancer develop-
ment, progression, and metastasis [127]. A combination of EGCG
and curcumin or EGCG, curcumin and lovastatin was able to reduce
cell viability and invasion in vitro in TE-8 and SKGT-4 esophageal
cancer cells through reduction of p-ERK1/2, c-Jun and COX-2, and
activation of caspase-3 whereas it inhibited tumor growth in vivo
through suppressing the expression of Ki67, p-ERK1/2 and COX-2
[32]. EGCG and doxorubicin mixture enhanced the inhibition of
metastatic tumor growth in PC-3ML prostate cancer cells [41].
EGCG, ascorbic acid, lysine, proline and arginine combination
inhibited cell proliferation and invasion through downregulation
of MMP-2 and MMP-9 expressions in LNCaP and DU-145 prostate
cancer cells [44]. In gastric cancer, xenograft angiogenesis and
tumor growth in BCG-823 cells were inhibited by a combination of
EGCG and docetaxel [40] or a mixture of EGCG and capetibibe
[38]. EGCG and ascorbic acid combination strongly suppressed pro-
gression, and metastasis through scavenging of reactive oxygen
species in SMMC-7721 hepatocellular carcinoma [136]. EGCG (in
green tea extract), ascorbic acid, lysine, proline and arginine mix-
ture inhibited critical steps of cancer development and spread,
such as MMP-2 and -9 secretions and invasion in T-24 bladder can-
cer cells [137].

In CSCs, EGCG was also found to inhibit migration and invasion,
for example, it inhibited growth, spheroid formation, migration
and invasion and downregulates Casp37, Bcl-2, Survivin, XIAP,
Vimentin, Slug, Snail and nuclear β-Catenin in PC-3 and LNCaP
CSCs [132]. In addition, EGCG inhibited self-renewal and migration
and reversed the epithelial–mesenchymal transition via NF-κB p65
inactivation in nasopharyngeal CNE2 and C666-1 CSCs [138].

Anticancer effects of EGCG combined with nanoparticles

On the other hand, nanotechnology mediated approaches to
develop drugs have attracted intense attention in cancer prevent-
ion and therapy research. Nanoparticles appears to hold great pro-
mise in the field of cancer management because of its unique physicochemical properties including nanometer size, large sur-
face area-to-mass ratio, and efficient interaction with cells [2]. Sid-
diqui et al envisioned that nanoparticle-mediated delivery could be
useful to control the toxicity and enhance the bioavailability of the
chemopreventive agents such as EGCG, and introduced the concept of
"nanochemoprevention" [26,49,139,140]. These studies demon-
strated that EGCG encapsulated in polymeric nanoparticles (NPs)
exhibited over ten-fold dose advantage for exerting its apoptotic
and effects against cancer, both in vitro and in vivo [26,49]. In
breast cancer, EGCG-Ptx-PLGA-Casein-NPs induce apoptosis in
MDA-MB-231 cells through inhibiting NF-κB activation [141].
EGCG-LDH nanohybrids induce apoptosis within over 5-fold dose
advantages in vitro compared to EGCG alone in prostate PC-3 can-
cer cells [142]. Similarly in PC-3, EGCG-PLA-PEG-NPs enhance
bioavailability and limited unwanted toxicity of EGCG within 10-
fold dose advantage [13] and induce apoptosis within remarkably
significant increase in pro-apoptotic Bax with a concomitant
decrease in anti-apoptotic Bcl-2 (Fig. 5), increase in poly(ADP-
ribose) polymerase (PARP) cleavage and marked induction of p21
and p27 [26]. In vivo oral administration of EGCG-CS-NPs induces
apoptosis in 22Rv1 prostate cancer cells increasing in Bax expres-
sion with a concomitant decrease in Bcl-2 and activation of cas-
pases [143]. Another study demonstrated apoptosis induction
(Bax, PARP) in tumors harvested from the treated mice within 8-
fold dose advantage of nanoformulation over native EGCC [144].
EGCG and HDHA-DOX-NPs combination induces apoptosis in Ehr-
lich’s ascites carcinoma (EAC) whereas EGCG enhances the anti-
cancer activities of HDHA-NPs significantly increasing the mean
survival time of the animals [145]. In vitro treatment of 20 μM of
EGCG-PLGA-PEG-DCL-NPs or EGCG-PLGA-PEG-AG-NPs into PC-3,
LNCaP and DU-145 prostate cancer cells induces apoptosis upregu-
lating Bax, DR5, and P27 and decreasing Bcl2 and survivin [89].

Moreover, EGCG-PLA-PEG-NPs inhibit proliferation in PC-3 prostate
cancer cells through upregulation of p21 and p27 [26]. Finally, EGCG-NPs inhibit cell proliferation through cell cycle regu-
latory proteins via downregulation of Cyclin A, Cyclin B1, Cyclin D3,
surviving, CDK2 and CDK6 and upregulation of P21 and P27 [49].

EGCG-NPs was also found to inhibit cancer angiogenesis and
metastasis such as EGCG-Ptx-PLGA-Casein-NPs which downregu-
lated the key genes associated with angiogenesis, tumor metastasis
and survival as well as induced apoptosis and inhibited NF-κB activ-
ation in MDA-MB-231 breast cancer cells [141].

Conclusion

Chemoprevention, also defined as “slowing the process of car-
icogenesis” concept appears to be a viable option for cancer con-
trol. To be effective, chemopreventive intervention should be
addressed during the early stages of the carcinogenesis process.
A plethora of experimental evidences suggest that both dietary and lifestyle factors act by balancing promotion/prevention of
chronic inflammation and/or oxidative stress, sometime leading
alterations associated with cancer initiation. Within the chemopre-
ventive armamentarium, the use of natural agents from dietary
sources is generally preferred with respect to bioactive molecules
deriving from other sources. Many of these natural occurring
agents demonstrated antioxidant activity, and compounds belong-
ing to polyphenols chemical class may play a promising role for
cancer prevention. Epidemiological studies conducted in humans
support the existence of an association between natural polyphe-
nols consumption and a reduced cancer risk. In the last decade, a
representative member of polyphenols, i.e. EGCG, has been the
focus of a number of studies scrutinizing its beneficial effects on
health. Therefore, consumption of green tea has become more and
more popular in the world due to its versatile health benefits
[29]. Moreover, interesting preclinical evidence and encouraging
initial clinical trials have been obtained testing EGCG as chemopre-
ventive agent. However, despite its beneficial therapeutic poten-
tial, EGCG presents important pharmacokinetics problems, due to
inefficient systemic delivery and bioavailability. In order to
improve the poor systemic bioavailability and cellular uptake of
EGCG, various strategies have been adopted, which include combi-
nation therapy or polytherapy that consumes EGCG with one or
more medications. In particular, nanotechnology approaches could
help overcome pharmacokinetics issues of EGCG by controlling its
toxicity and enhancing its bioavailability to introduce the concept
of “nanochemoprevention” [26,49,139,140]. In addition, recent
studies conducted implying both EGCG and CSCs to found that
EGCG induces multiple of anticancer effects in CSCs and enhances
the chemo-sensitivity of chemo-drugs in CSCs.

In this review the current available studies of the anti-cancer
effects of EGCG alone and combined with other dietary and phar-
macetical agents as well as the recent novel nanotechnology
approaches used to deliver sustained levels of EGCG have been
covered and discussed in order to introduce some furnish driving
force for further evolution of research on innovative database able
to consolidate the chemopreventive potential of EGCG.

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