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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.


**Contents**



## 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 ailment 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

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**Fig. 1.** Schematic drawing of green tea leaves composition.

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 incipience 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

**Table 1**
Dried green tea composition.

| Molecular group | Component | | Molecular Formula | MW (g/mol) | Percent of dried tea extract | Main Biological effects |
|---|---|---|---|---|---|---|
| Polyphenols | Catechins | Epicatechin | $C_{15}H_{14}O_6$ | 290.26 | 30–42 | Cancer prevention, antioxidant, antibacterial and antiviral effects. |
| | | Epicatechin-3-gallate | $C_{22}H_{18}O_{10}$ | 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 | $C_{15}H_{10}O_6$ | 286.23 | 5–10 | Anti-histamine and anti-inflammatory effects. |
| | | Quercetin | $C_{15}H_{10}O_7$ | 302.236 | | |
| | | Myricetin | $C_{15}H_{10}O_8$ | 318.2351 | | |
| | Depsides | Theogallin | $C_{14}H_{16}O_{10}$ | 344.27 | 2–4 | Inhibition of Influenza A viruses. |
| | | Chlorogenic acid | $C_{16}H_{18}O_9$ | 354.31 | | |
| | | Coumarylquinic acid | $C_{16}H_{18}O_8$ | 338.312 | | |
| Organic acids | Ascorbic acid | | $C_6H_8O_6$ | 176.124 | 1–2 | Anticancer effects. |
| | Gallic acid | | $C_7H_6O_5$ | 170.12 | 0.5 | |
| | Quinic acid | | $C_7H_{12}O_6$ | 192.17 | 2 | |
| | Folic acid | | $C_{19}H_{19}N_7O_6$ | 441.404 | 0.5 | |
| | Other organic acids | | – | – | 4–5 | |
| Amino acids | Theanine | | $C_7H_{14}N_2O_3$ | 174.2 | 4–6 | Neuronal cell protection and relaxation effect. |
| | γ-aminobutyric acid | | $C_4H_9NO_2$ | 103.121 | 2–4 | Decrease of blood pressure. |
| Methylxanthines | Caffeine | | $C_8H_{10}N_4O_2$ | 194.19 | 7–10 | Increased alertness and a mild diuretic effects. |
| | Theobromine | | $C_7H_8N_4O_2$ | 180.164 | | |
| | Theophylline | | $C_7H_8N_4O_2$ | 180.167 | | |
| Carbohydrates | Glycosides | | – | – | 10–15 | Energy and prevent blood sugar increase. |
| Minerals | Aluminium, fluorine, manganese, iron, magnesium, potassium, phosphorus, zinc, selenium and sodium. | | – | – | 6–8 | Regulators. |
| Volatiles | Saponin | | $C_{58}H_{94}O_{27}$ | 1223.363 | 0.02–1 | Anti-fungal, anti-inflammatory, and anti-allergy properties. |
| | Linalool | | $C_{10}H_{18}O$ | 154.25 | | |
| | △-Cardinene | | $C_{15}H_{24}$ | 204.357 | | |
| | Geraniol | | $C_{10}H_{18}O$ | 154.253 | | |
| | Nerolidol | | $C_{15}H_{26}O$ | 222.37 | | |
| | α-Terpineol | | $C_{10}H_{18}O$ | 154.25 | | |
| | Cis-Jasmone | | $C_{11}H_{16}O$ | 164.246 | | |
| | Indole | | $C_8H_7N$ | 117.15 | | |
| | β-Inone | | $C_{13}H_{20}O$ | 192.302 | | |
| | 1-Octanal | | $C_8H_{16}O$ | 128.215 | | |
| | Indole-3-Carbinol | | $C_9H_9NO$ | 147.18 | | |
| | β-Caryophyllene | | $C_{15}H_{24}$ | 204.36 | | |
| Vitamins | Thiamine (B1) | | $C_{12}H_{17}N_4OS^+$ | 265.355 | – | Maintenance of healthy skin and mucus membrane. |
| | Riboflavin (B2) | | $C_{17}H_{20}N_4O_6$ | 376.369 | | |
| | Niacin (B3) | | $C_6H_5NO_2$ | 123.111 | | |
| | Vitamin B6 | | $C_8H_{11}NO_3$ | 169.18 | | |
| | Vitamin E | | $C_{29}H_{50}O_2$ | 430.717 | | |
| | β-Carotene | | $C_{40}H_{56}$ | 536.888 | | |
| Chlorophyll | – | | $C_{55}H_{72}O_5N_4Mg$ | 893.509 | – | Deodorizing effect, kidney stone prevention and strengthens immune system. |

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.

## EGCG 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 characteristicsof 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

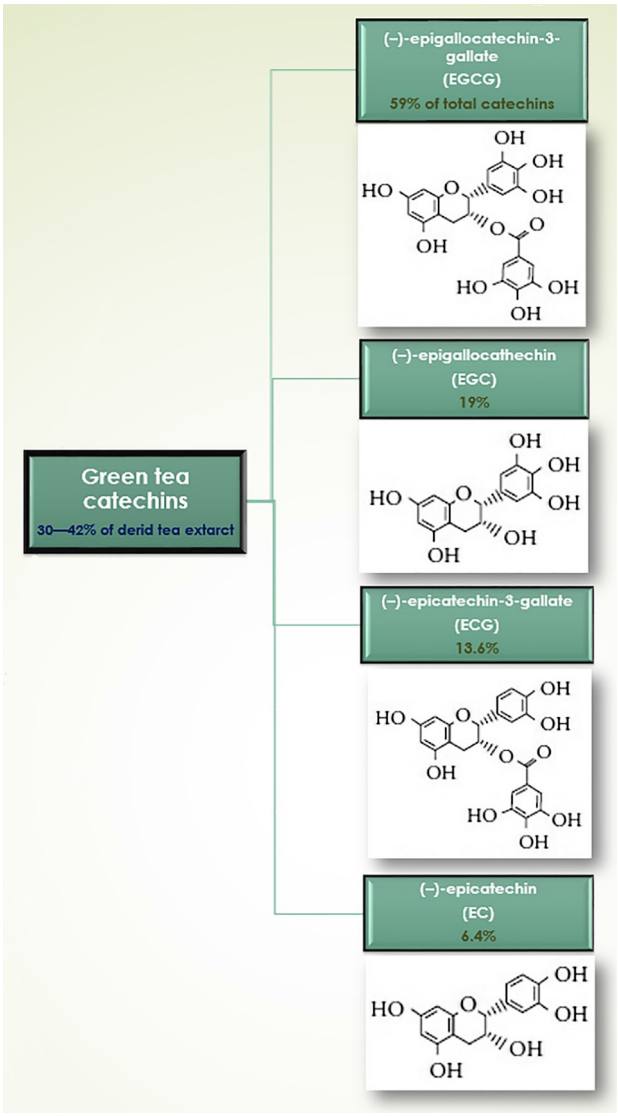



**Fig. 2.** Molecular structure green tea catechins.

bind to their cell surface receptors TNFR1 and TNFR2, death receptor DR4 and DR5 and Fas causing sequential activation of Caspase-8, Caspase-3 and Caspase-7 [58]. Moreover, apoptosis is regulated by several proteins such as BCL-2 [59], BAX [60], BCL-XL [61], BCL-XS [62] BAD [63], BAK [64], BID [65], BIM [66], PUMA [67], XIAP [68], NOXA [69], SMAC [70], MCL-1 [71] and c-FLIP [72].

EGCG induced cell apoptosis (Table 3) through intrinsic mitochondrial pathway via activation of Caspase-9 in PC3 prostate cancer cells [47], MCF-7 breast cancer cells [73] and PANC-1, MIA-Pa-Ca-2, Hs 766 T and AsPC-1 pancreatic cancer cells [48]. EGCG has also been shown to induce apoptosis through extrinsic death receptor pathway in MIA-Pa-Ca-2 pancreatic cancer cells via activation of Fas, DR5 and Caspase-8 [74]. In addition, EGCG downregulated the expression of anti-apoptotic proteins, such as BCL-2 in PANC-1, MIA-Pa-Ca-2, Hs 766 T and AsPC-1 pancreatic cancer cells [48], MDA-MB-231 breast cancer cells [75], NCI-H295 adrenal cancer cells [76] and PC-12 pheochromocytoma cells [77], BCL-XL in PANC-1, MIA-Pa-Ca-2, Hs 766 T and AsPC-1 cells pancreatic cancer cells [48] and NCI-H295 adrenal cancer cells [76], survivin in MCF-7 breast cancer cells [73] and NUGC-3 gastric cancer cells [78]; and XIAP in NCI-H295 adrenal cancer cells [76]. Also, EGCG was found to upregulate the expression of pro-apoptotic proteins, including Apaf-1 and BAD in NCI-H295 adrenal cancer cells [76] and BAK, BAX, BCL-XS and PUMA in PANC-1, MIA-Pa-Ca-2, Hs 766T and AsPC-1 pancreatic cancer cells [48]. Moreover, EGCG induced apoptosis through both intrinsic and extrinsic pathways, regulatory proteins and endoplasmic reticulum stress via activation of caspase-dependent, caspase-independent, death receptors, down-regulation of anti-apoptotic proteins BCL-2, BCL-XL and XIAP and upregulation of pro-apoptotic BAD and BAX in NCI-H295 human adrenal cancer cells [76].

pEGCG is synthesized by modifying reactive hydroxyl groups with peracetate groups and found to be converted as well as accumulated into parental EGCG when cultured with MDA-MB-231 human breast cancer cell. pEGCG was found to inhibit significantly tumor growth *in vivo* through apoptosis induction in tumor tissues [79].

### *Modulation of cellular proliferation*

Proliferation is an important part of cancer development and progression manifested by altered expression and/or activity of cell cycle related proteins [80]. Similarly, cell cycle is the process by which cells progress and divide [2]. Cell cycle regulatory proteins include cyclins, cyclin-dependent kinases (Cdks), CDK interacting proteins (CIPs) such as p21, kinase inhibitory proteins (KIPs) such as p27, Cdk inhibitors (INKs) such as p18 and other proteins, such as p53 and survivin [80–83]. In cancer however this regulatory process malfunctions which results in uncontrolled cell proliferation and ultimately growth and progression of the tumor [2]. Many evidences are available where EGCG has been shown to regulate the cell cycle machinery via cell cycle regulatory proteins, leading to cell cycle arrest and inhibition of cellular proliferation.

EGCG can induce mostly G0/G1 cell cycle arrest [45,48,84–87] while its combination with other agents has been shown to induce G0/G1 [46], G2/S [45] and/or G2/M [43] cell cycle arrest in variety of cancer models. In addition, EGCG induces G1 cell cycle arrest through regulation of cyclin D1, cdk4, cdk6, p21 and p27 in AsPC-1, Hs 766T, PANC-1 and MIA-Pa-Ca-2 pancreatic cancer cells [48]. Similarly, EGCG inhibits cell proliferation of A549, H460 and H1650 lung cancer cells through induction of G0/G1 cell cycle arrest via inhibiting EGFR/cyclin D1 signaling [86]. Likewise, EGCG inhibits cell proliferation in LNCaP and DU-145 prostate cancer cells via cell-type-specific manner which may be mediated by WAF1/p21-causing G0/G1-phase cell-cycle arrest [87]. In addition, EGCG induces G1 cell cycle arrest in HeLa and CaSki cervical cancer cells trough gene expression regulation [85,88]. Moreover, EGCG also suppresses cyclin D1 and activate p21 via ERK, IKK and PI3K signaling pathway in order to inhibit cell proliferation in HCT-116, Caco-2, HT-29 and SW480 colorectal cancer cells [89]. EGCG also induces cell cycle arrest in A431 skin cancer cells through inhibition of Cip1/p21 without any changes in Kip1/p27, CDK2, and cyclin D1 while there was a decrease in CDK4 only at low doses [90,91].

### *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

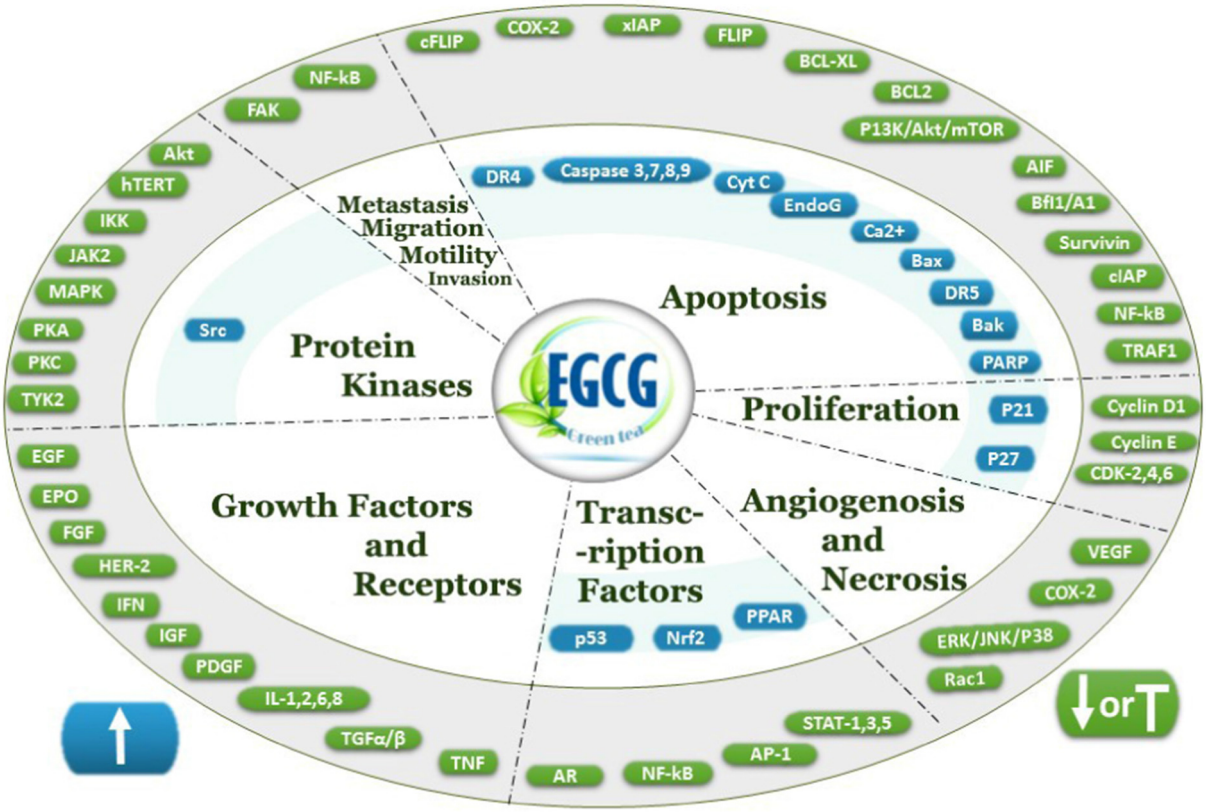



**Fig. 3.** Schematic drawing of the regulative actions of EGCG. This carton is based on the available literature about the anticancer effects of EGCG.

[96–98]. 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 trough downregulation of VEGF expression in Hs578T breast [130]. In NF639 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 invasion, motility and migration in MDA-MB-231 through inhibition of EGF-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-κB pathways [117]. Moreover, EGCG inhibited inhibits liver metastasis *in vivo* RKO colorectal cancer cells experiments and suppresses angiogenesis and induces apoptosis

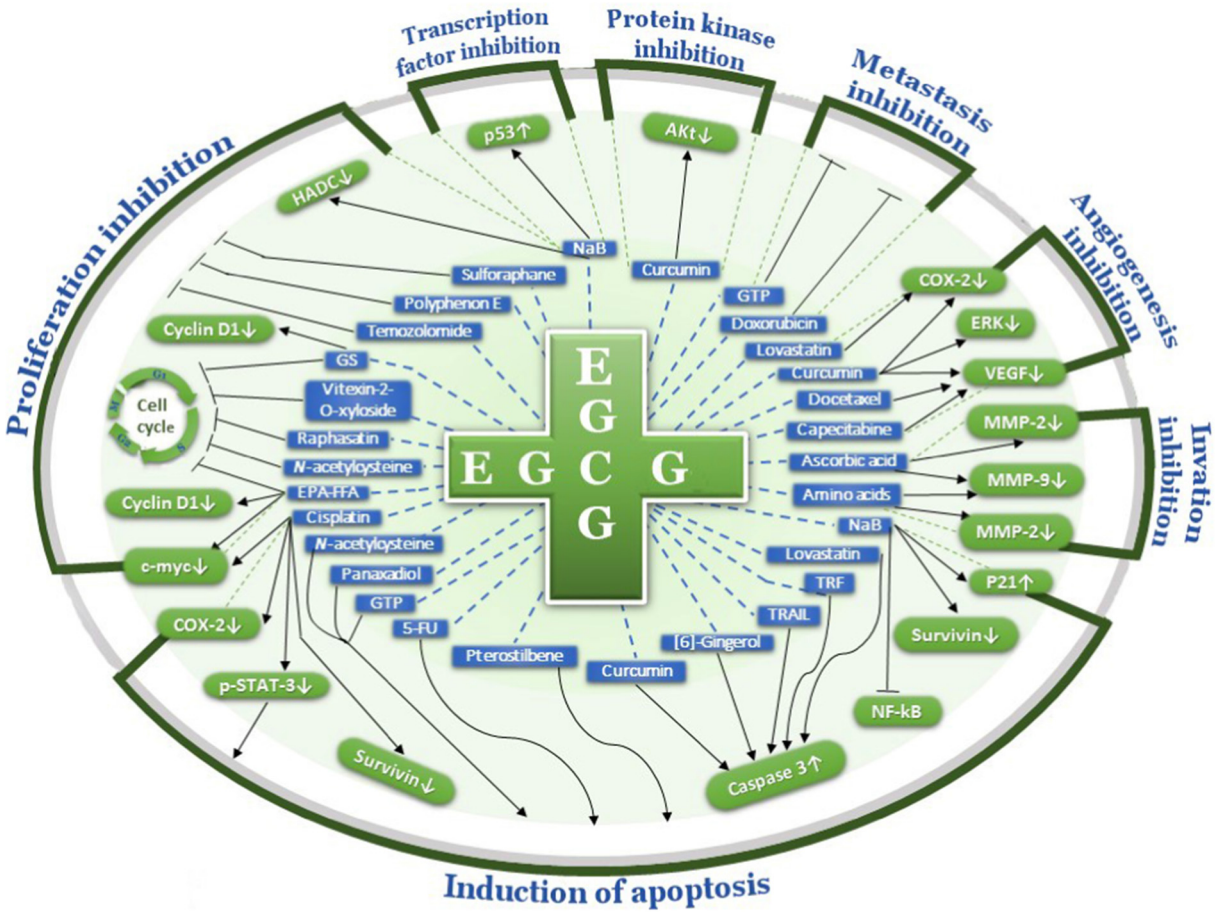



**Fig. 4.** Schematic drawing of the regulative actions of EGCG combined with other dietary and pharmaceutical agents. This carton is based on the available literature.

in liver metastasis [118]. EGCG inhibited Met signaling which helps to attenuate tumor spread/metastasis, independent of $H_2O_2$-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-κB 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 vivo* [123]. In BCaPT10 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].

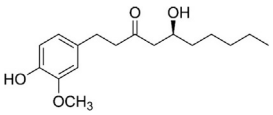
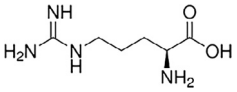
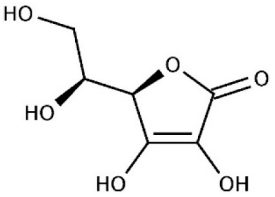
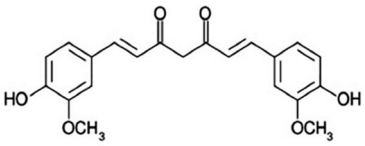
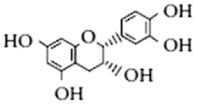
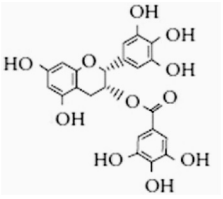
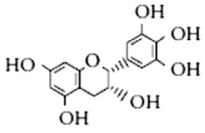
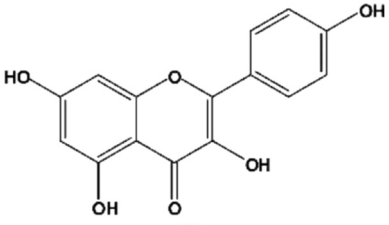
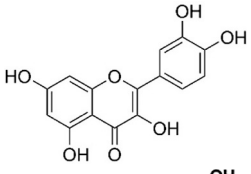
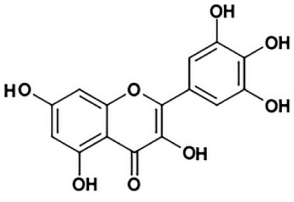
## Anticancer effects of EGCG combinations

### *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*-acetylcysteine (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

**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 | |  | $C_6H_{14}N_4O_2$ | 174.204 | Prostate (PC-3, LNCaP and DU-145) [44] and bladder (T-24) [137] cancers |
| Ascorbic acid | |  | $C_6H_8O_6$ or $HC_6H_7O_6$ | 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 |  | $C_{15}H_{14}O_6$ | 290.26 | Prostate (LNCaP) cancer [147] |
| | Epicatechin-3-gallate |  | $C_{22}H_{18}O_{10}$ | 442.37 | |
| | Epigallocatechin |  | $C_{15}H_{14}O_7$ | 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 |  | $C_{15}H_{10}O_8$ | 318.2351 | Prostate (LNCaP) cancer [147] |

(*continued on next page*)

**Table 2** (*continued*)

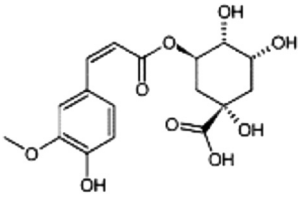
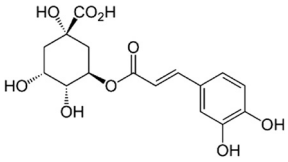
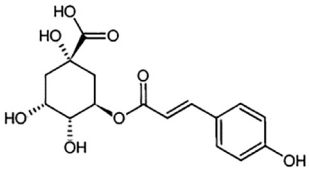
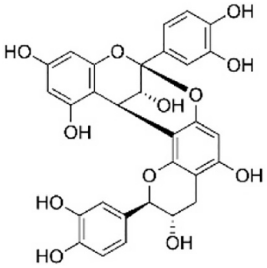
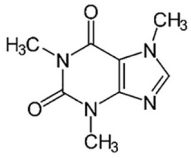
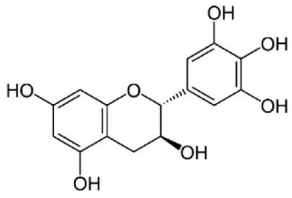
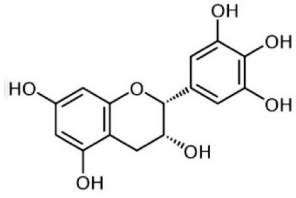
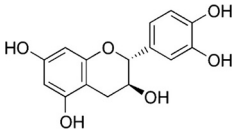
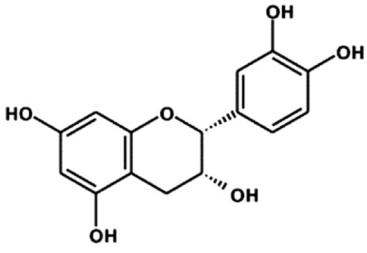
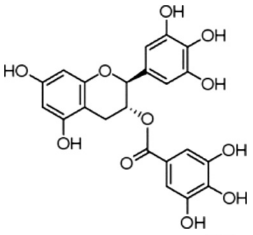
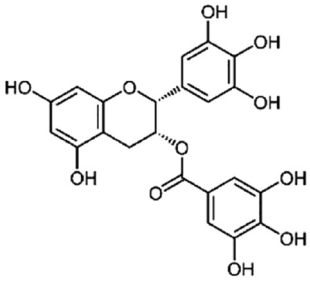
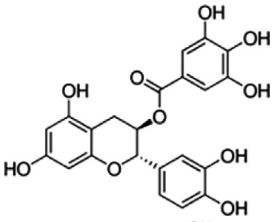
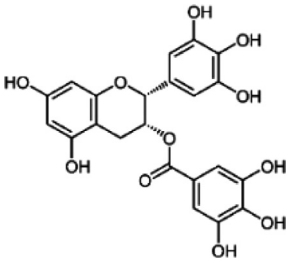
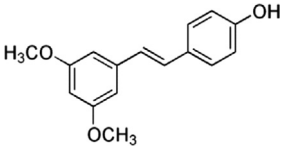
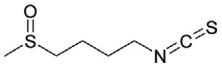
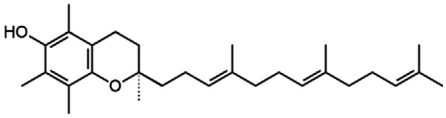
| | | Molecular structure | Molecular Formula | MW (g/mol) | Cancers (cell lines) |
|---|---|---|---|---|---|
| | Theogallin |  | $C_{14}H_{16}O_{10}$ | 344.27 | |
| | Chlorogenic acid |  | $C_{16}H_{18}O_9$ | 354.31 | |
| | Coumarylquinic acid |  | $C_{16}H_{18}O_8$ | 338.312 | |
| GS | |  | $C_{31}H_{28}O_{12}$ | 592.553 | Colorectal (HCT-116 and SW480) cancer[128] |
| Polyphenon E | Caffeine |  | $C_8H_{10}N_4O_2$ | 194.194 | Lung cancer [148] |
| | (+)-Gallocatechin |  | $C_{15}H_{14}O_7$ | 306.27 | |
| | EGC |  | | | |
| | (+−)-Catechin |  | $C_{15}H_{14}O_6$ | 290.271 | |
| | EC |  | | | |

**Table 2** (*continued*)

| | | Molecular structure | Molecular Formula | MW (g/mol) | Cancers (cell lines) |
|---|---|---|---|---|---|
| | (−)-Gallocatechin gallate |  | $C_{22}H_{18}O_{11}$ | 458.375 | |
| | ECG |  | | | |
| | (−)-Catechin gallate |  | $C_{22}H_{18}O_{10}$ | 442.376 | |
| | EGCG |  | | | |
| pterostilbene | |  | $C_{16}H_{16}O_3$ | 256.301 | Pancreatic (PANC-1 and MIA-Pa-Ca-2) cancer [36] |
| Sulforaphane | |  | $C_6H_{11}NOS_2$ | 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] |

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 3**
Anticancer effects of EGCG alone and combination.

| 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 [75]; 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 stimulation of pro-apoptotic signaling and downregulation of MMP-9 expression [75]. 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] | Inhibit 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 | – | Induce apoptosis, inhibite NF-κB activation and downregulate the key genes associated with angiogenesis, tumor metastasis and survival [141]. |
| | | EGCG-LbL-PSS/PAH-NPs | 1 or 5 μM [152] | Inhibit HGF-induced c-Met signaling after prolonged pre-incubation [13,152]. |
| | MCF-7 | 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] | Induces growth inhibition and apoptosis through surviving expression downregulation via suppressing AKT pathway and activation of caspase-9 [73]. Inhibits cell migration and invasion through downregulation of VASP expression and Rac1 activity [109]. Inhibits nicotine and estradiol-induced cell proliferation via downregulation of α9-nicotinic acetylcholine receptor signaling pathway [153]. Inhibits cell viability and proliferation through epigenetic repression of hTERT [150], inhibition of glucose uptake and metabolism [151], epigenetic downregulation of ER-α via p38MAPK/CK2 activation [154] and activation of Cav3.2 channels via elicit of Ca2 + spike [146]. |
| | | 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 | EGCG | 10 μM | Inhibits cell proliferation and migration trough downregulation of VEGF expression [155]. |
| | 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]. |
| | NF639 | 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]. Inhibit branching colony growth and cell invasion through induction of estrogen receptor α expression via activating FOXO3a signaling [108]. |
| | 4 T1 | EGCG | 10 mg/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 | 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 | 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-1via suppressing HIF-1α and VEGF protein expression [103,104]. Inhibits cell proliferation through upregulation of endostatin expression and suppression of VEGF expression [102] and suppressing of the expression of the cell death-inhibiting gene, Bcl-xL [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 proteasomal 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-1a protein expression and HIF-1a dependent expression of VEGF, IL-8, and CD31 as well as activation of Akt [104]. Inhibits cancer chemo-resistant variants through downregulation of Axl and Tyro 3 expression [160]. Inhibits nicotine-induced migration, invasion and upregulation of HIF-1α, VEGF, COX-2, p-Akt and p-ERK [105]. |
| | | 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] | Inhibit cell growth *in vitro* and *in vivo* through induction of cell cycle arrest at G1 and S/G2 phases via downregulating cyclin D1 and cyclin B1 [45]. |
| | CL13 | EGCG | 5,10,25 and 50 | Suppresses cancer cell growth through upregulating miR-210 expression caused by stabilizing HIF-1α [162]. |
| | | EGCG + *N*-acetylcysteine (NAC) | (0–100) μM of EGCG in the presence or absence of 0–2 mM NAC. | EGCG and NAC interact to form EGCG-2′-NAC adduct which induces cell culture apoptosis [126]. |
| | H1299 | EGCG | 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]. |
| | H460 | EGCG | 1,5,10,20 and 40 μM [159]. 10–40 μM [86]. 80 μM [160]. 5,10,25 and 50 [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 proteasomal 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]. Inhibit cancer cells proliferation including their chemo-resistant variants through downregulation of Axl and Tyro 3 expression [160]. 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] | 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 proteasomal 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]. |
| | H1299 | EGCG | 5,10,50 and 100 μM [106] | 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]. |
| | Lu99 | EGCG | | Reduces cell motility *in vitro* wound healing assay. Increases Young's modulus of Lu99 from 1.29 to 2.28 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 & $IC_{50}$ | Biological effects |
|---|---|---|---|---|
| | H69<br>H69VP | EGCG | 20,40,50,60,80,100,120,140,150 and 200 μM. $IC_{50}$: ~70 μM (24 h) | Induces cell apoptosis, reduces telomerase activity and inducts a cell-cycle block in S phase [164]. |
| | NCI-H460 | EGCG | 10,25,50 and 100 *in vitro* [104] | Inhibits HPV-16 oncoprotein induced angiogenesis conferred by cancer cells through the inhibition of HIF-1a protein expression and HIF-1a dependent expression of VEGF, IL-8, and CD31 as well as activation of Akt [104]. |
| | | EGCG + Curcumin | 10,20,40 μM EGCG and/or the same concentrations for curcumin | Inhibit cell growth *in vitro* and *in vivo* through induction of cell cycle arrest at G1 and S/G2 phases via downregulating cyclin D1 and cyclin B1 [45]. |
| | – | EGCG + Polyphenon E | Benzo(*a*)pyrene [B(*a*)P]-induced lung cancer in female A/J mice (100 mg/kg). | Mixture inhibits significantly pulmonary adenoma formation and growth *in vivo* [148]. |
| **Pancreatic cancer** | AsPC-1<br>Hs 766 T | 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-indepdendent apoptosis signaling, inhibition of Ras/Raf-1/ERK1/2 signaling, induction of MEKK1, JNK1/2 and p38 MAPK activities [48]. |
| | PANC-1 | EGCG | 5–80 μM [48] | |
| | | EGCG + Pterostilbene | 20, 30 and 40 μM EGCG with/without 30 μM Pterostilbene | 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]. |
| | MIA-Pa-Ca-**2** | EGCG | 10, 100 and 1000 μM, $IC_{50}$ below 50 μM [165]; 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-indepdendent apoptosis signaling, inhibition of Ras/Raf-1/ERK1/2 signaling, induction of MEKK1, JNK1/2 and p38 MAPK activities [48]. Inhibits Hsp90 function by impairing Hsp90 association with co-chaperones resulting anti-proliferating effects [165]. |
| | | EGCG + TRAIL | 50 μg/ml E+5 ng/ml T | A synergistic increase in apoptosis and cleavage of procaspase-3. Furthermore, clonogenic cell survival assay demonstrates the significant diminishment of cancer cell proliferation in the presence of both EGCG and TRAIL [74]. |
| | | EGCG + Pterostilbene | 20, 30 and 40 μM EGCG with/without 30 μM Pterostilbene | 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]. |
| **Ovarian cancer** | SKOV3 | EGCG | 20,30,40 and 50 μg/mL [166]; 20,40,60,80,100 and 120 μg/mL [167]; 100 μM [107] | Inhibits cell proliferation and induces apoptosis through inhibition of cell cycle and DNA synthesis inducting NDA damage [166]. Downregulates AQP5, nuclear p65 and Iκ-Bα expressions [167]. Inhibit cell motility via suppression of Hsp90 chaperone system [107]. |
| **Oral cancer** | SAS<br>Cal-27<br>Ca-922 | 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-δ-STAT1 signaling pathway [168]. |
| | SCC-9 | EGCG | 5,10,15 and 20 μM *in vitro*; 10 and 20 mg/day/kg 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]. |
| | SCC-4 | 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-δ-STAT1 signaling pathway [168]. Suppresses cell proliferation and promotes apoptosis and autophagy through upregulation of BAD, BAK, FAS, IGF1R, WNT11, and ZEB1 genes expressions and downregulation of CASP8, MYC, and TP53 [169]. |
| | KB | 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]. |
| | 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-δ-STAT1 signaling pathway [168]. Inhibits cancer invasion via repressing functional invadopodia formation [113]. |
| | 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 and FAK/Src signaling [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<br>SNU-1066 | 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** | ($Oct4^{high}$/$Nanog^{high}$/β-$catenin^{high}$/$ABCG2^{high}$/$MRP\text{-}1^{high}$/$MDR\text{-}1^{high}$) in TW01 CSCs<br>($Oct4^{high}$/$Nanog^{high}$/β-$catenin^{high}$/$ABCG2^{high}$/$MRP\text{-}1^{high}$/$MDR\text{-}1^{high}$) 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 EGCG 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]. |

| | | | | |
|---|---|---|---|---|
| | CNE2 | EGCG + Cisplatin | EGCG (20 μM) + Cisplatin (10 μM) were injected subcutaneously into the flanks of nude mice and allowed to grow for 8 weeks | EGCG increases chemo-sensitivity of cisplatin *in vivo* [138]. |
| | $CD44^+$ in CNE2 CSCs | EGCG | 25,50 and 75 μM | Inhibits nasopharyngeal cancer stem cell self-renewal and migration and reverses the epithelial–mesenchymal transition via NF-κB p65 inactivation [138]. |
| | C666-1 | EGCG + Cisplatin | EGCG (20 μM) + Cisplatin (10 μM) were injected subcutaneously into the flanks of nude mice and allowed to grow for 8 weeks | EGCG increases chemo-sensitivity of cisplatin *in vivo* [138]. |
| | $CD44^+$ in C666-1 CSCs | EGCG | 25,50 and 75 μM | Inhibits nasopharyngeal cancer stem cell self-renewal and migration and reverses the epithelial–mesenchymal transition via NF-κB p65 inactivation [138]. |
| **Gastric cancer** | BGC-823 | EGCG | 1.5 mg/d IP injection for 56 days | Inhibits xenograft angiogenesis and tumor growth [40]. |
| | | EGCG + Docetaxel | – | |
| | | EGCG + Capecitabine | 200 mg/kg capecitabine daily by oral gavage + EGCG (IP injection of 1.5 mg EGCG daily | Inhibits xenograft angiogenesis and tumor growth [38]. |
| | AGS | EGCG | 5,10,25 and 50 μM *in vitro* and 50 μM EGCG + AGS cells *in vivo* into BALB/c nude female mice for 7 days [114]; 20,40,60,80,120 and 240 μg/mL [171] | 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]. |
| | AZ521 | EGCG | 5,10,20 and 40 μM | Inhibits cell proliferation through downregulation of DEAD-box RNA helicase p68 [172]. |
| | NUGC-3<br>MKN-1<br>MKN-28<br>MKN-45<br>TMK-1 | EGCG | 25,50,75 and 100 μM | Induces cell apoptosis through inhibition of survivin expression downstream of p73 [78]. |
| | SGC-7901 | EGCG | 1.5 mg/d IP injection into female BALB/c nude for 28 days | Inhibit tumor growth and angiogenesis through reducing VEGF-induced endothelial cell proliferation, migration and tube formation [115]. |
| **Hepatocellular Carcinoma** | Hepa 1c1c7 | EGCG | 100 μM | Inhibit cell motility via suppression of Hsp90 chaperone system [107]. |
| | SMMC-7721 | EGCG + Ascorbic acid | – | Mixture strongly suppress proliferation and metastasis through scavenging of reactive oxygen species [136]. |
| | HepG2 | EGCG | 15,30,60,120 and 240 | Induces non-apoptotic cell death via ROS-mediated lysosomal membrane permeabilization [173]. |
| | | EGCG + 5-FU | 5-FU (0.05 μg) and EGCG (25 μmol) | Combination significantly decreased the viability of cells, compared with EGCG or 5-FU-treated cells [174]. |
| | CD133 and NANOG in HepG2 cancer stem cells | EGCG | 10 and 20 μM | Inhibit sphere formation through inhibition of CD133, Nanog, ABCC1, ABCG2, Nek2 and p-Akt [174]. |
| **Squamous cell carcinoma** | SCC VII/SF | EGCG | 5,10,20,40,80,100,150 and 200 μM *in vitro*; 25,50 and 75 mg/kg/day IP injection into the flank of syngeneic C3H/HeJ micefor 21 days | Inhibits HGF-induced cell growth and invasion through suppression of HGF/c-Met signaling pathway while it inhibits xenograft tumor growth *in vivo* via rising apoptosis [112]. |
| **Prostate cancer** | PC-3 | EGCG | 0–50 μM. $IC_{50}$ : 39.0 μM | Antiproliferative effects through ERK1/2 activation via MEK-independent, PI3-K-dependent signaling pathway [175]. |
| | | | 1 and 25 μM. $IC_{50}$: 25 μM | Induces cell apoptosis through upregulation of caspase-9a expression [47]. |
| | | EGCG + Curcumin | 50 and 100 μM E and/or 50 μM C | Induction of cell cycle arrest at both S and G2/M phases via upregulating p21 protein level [135]. |
| | | EGCG + Quercetin | 80 μM EGCG and/or 10 and 20 μM Quercetin | Mixture demonstrates enhanced inhibition of cell proliferation and induction of cell apoptosis *in vitro* by increasing the intracellular concentration of EGCG and decreasing EGCG methylation [33]. |
| | | EGCG + Sulforaphane | 20 and 100 μM E and/or 25 μM S | Reduction of cell viability via inhibition of AP-1 activation [34]. |
| | | EGCG + Ascorbic acid + Lysine + Proline + Arginine | 50 microg/mL-500 μg/mL of the mixture | Combination inhibits cell proliferation and invasion through downregulation of MMP-2 and MMP-9 expressions [44]. |
| | | EGCg-$^{198}$AuNPs | single-dose intra-tumoral administration in human prostate cancer-bearing SCID mice | 80% reduction of tumor volumes after 28 d demonstrating significant inhibition of tumor growth compared to controls [176]. |
| | | EGCG-LDH nanohybrids | 25,50,75 and 100 μM/L; $IC_{50}$: 16.66 μM/L (24 h), 15.47 μM/L (48 h), 16.33 μM/L (72 h) | Induce apoptosis within over 5-fold dose advantages compared to EGCG alone in *in-vitro* system [142]. |

(*continued on next page*)

**Table 3** (*continued*)

| Cancers | Cell lines | EGCG Combination | Dose & $IC_{50}$ | Biological effects |
|---|---|---|---|---|
| | | EGCG-PLA-PEG-NPs | 0.7,1.37,2.74 and 5.48 μmol/L *in vitro*, $IC_{50}$: 3.74 μmol/L (24 h); *in vivo*, mice each received 100 μg dissolved in PBS thrice weekly [26] | 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 [26]. |
| | | EGCG-PLGA-PEG-DCL-NPs<br>EGCG-PLGA-PEG-AG-NPs | 20 μM | *In vitro*, 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]. |
| | PC-3ML | EGCG + Doxorubicin | 30 and 60 μM E + D *in vitro*; 0.14–57 mg/kg E and/or 2 mol/L–0.07 mg/kg D into immunodeficiency mice | Combination enhances the inhibition of metastatic tumor growth [41]. |
| | ($CD44^+CD133^+$in PC-3) CSC | 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]. |
| | LNCaP | EGCG | 12 μM [177]; 20,40 and 80 μM [178]; 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 [87].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]. |
| | | Green tea polyphenols (GTP) | 10–80 μg/mL | *In vitro* and *in vivo* inhibition of testosterone-mediated induction of ornithine decarboxylase1 [147]. |
| | | EGCG + Quercetin | 80 μM EGCG and/or 10 and 20 μM Quercetin | 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]. |
| | | EGCG + Ascorbic acid +Lysine+Proline+Arginine | 50 microg/mL–500 μg/mL of the mixture | Combination inhibits cell proliferation and invasion through downregulation of MMP-2 and MMP-9 expressions [44]. |
| | | EGCG-PLGA-PEG-DCL-NPs<br>EGCG-PLGA-PEG-AG-NPs | 20 μM | *In vitro*, 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]. |
| | ($CD44^+CD133^+$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 [87].<br>Inhibit cell motility and invasion through inhibition of c-Met signaling via altering the structure or function of lipid rafts [122]. |
| | | EGCG + Ascorbic acid + Lysine + Proline + Arginine | 50 microg/mL–500 μg/mL of the mixture | Combination inhibits cell proliferation and invasion through downregulation of MMP-2 and MMP-9 expressions [44]. |
| | | EGCG-PLGA-PEG-DCL-NPs<br>EGCG-PLGA-PEG-AG-NPs | 20 μM | *In vitro*, 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]. |
| | 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 | 86.7 mg/kg/d IP injection into nude mice for 20 days. | 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 | 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 [143]. |
| | – | EGCG | Five-week-old male TRAMP offspring were fed AIN-76A diet and 0.06% EGCG in tap water for28 weeks | Inhibits cell proliferation and induces apoptosis through downregulation of AR, IGF-1, IGF-1R, p-ERK 1/2, COX-2, and iNOS [179]. |

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|---|---|---|---|---|
| | – | GTP | – | *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]. |
| **Melanoma** | Mel 928 | EGCG-CS-NPs | 0.5,1.0,2.0,4.0 and 8.0 μM *in vitro*; $IC_{50}$: 7 μM (48 h). 100 μg/mice;120 μL treatment volume into Athymic (nu/nu) male nude mice. | Induct 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]. |
| **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 | Inhibit cell viability and proliferation *in vitro* and *in vivo* within a highly biocompatible and biodegradable EGCG-coated MSN nanoparticles [180]. |
| **Cervical cancer** | HeLa | EGCG | 10, 25, 50 and 100 μM [88]; 10,20,30,40,50,60,70,80,90 and 100 μM [85]; $IC_{50}$: 47.9 μM [88]; 100 μM (24 h) and 50 μM (48 h) [85]. | 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]. |
| | CaSki | EGCG | 10, 25, 50 and 100 μM. $IC_{50}$: 27.3 μM (24 h) | Cell growth inhibition trough gene expression regulation and induction of cell cycle arrest [88]. |
| **Colorectal cancer** | HCT-116 | 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]. $IC_{50}$: 3 μM [119] | Suppresses cancer cells growth through cyclin D1 degradation and p21 transcriptional activation via ERK, IKK and PI3K signaling pathway [89]. Inhibits Met signaling [119] which helps to attenuate tumor spread/metastasis, independent of $H_2O_2$-related mechanisms [120]. Inhibits cell proliferation through inhibition of HGF-induced Met/ERK/AKT signaling pathway [119]and through inhibition of Akt, activation and induction of p38 MAPK activation [118]. Induces cell apoptosis through cancer-specific induction of ROS and epigenetic modulation of expression of apoptosis-related genes, such as hTERT [181]. |
| | | EGCG + Panaxadiol | E (0,10,20 and 30 μM) and/or P (0,10 and 20 μM) | Inhibit cell proliferation and induce cell cycle arrest [35]. |
| | | EGCG + EPA-FFA + GS | EGCG (0–175 μM) + EPA-FFA (0–150 μM) + GS extract (0–15 μM) for 24 h | 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]. |
| | | 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]. | 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]. |
| | | EGCG + NaB | 10 μM E +(1,2,3,4,5 and 6 mM) N. $IC_{50}$: 10 μM E + 5 mM N | The combination treatment induces apoptosis and G2/M cell cycle arrest through decrease in HDAC1, DNMT1, survivin and HDAC activity [43]. |
| | CD133 and NANOG in HCT-116 stem cells | EGCG | 10 and 20 μM | Inhibit sphere formation through inhibition of CD133, Nanog, ABCC1, ABCG2, Nek2, and p-Akt [174]. |
| | CD44, CD133 and ALDH1 in HCT-116 stem cells | EGCG | 50, 100, 200 and 400 μM | Induces apoptosis and cell cycle arrest, attenuate spheroid formation and enhance chemosensitivity of 5-FU *in vivo* [37]. |
| | HCT-8 | EGCG | 10,20 and 35 μg/mL [182] | Inhibits proliferation *in vitro* and *in vivo*, induces apoptosis and affects cell cycle of cancer cells via inhibiting of HES1 and Notch2 expressions [182]. |
| | Caco-2 | EGCG | 1, 5 and 10 μM [183]; 1, 10 and 50 μM [89] | Induces cell growth inhibition as EGCG and 67LR at a physiological concentration can activate myosin phosphatase by reducing MYPT1 phosphorylation [183] or through cyclin D1 degradation and p21 transcriptional activation via ERK, IKK and PI3K signaling pathway [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); $IC_{50}$: 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-CS-CPP-NPs | 0.063, 0.125 and 0.250 mg/mL | Nanoparticles enhance stability, penetration and transportation of EGCG through cancer cells [184]. |
| | HT-29 | 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 mg/kg/d oral gavage to male BALB nude mice for 28 days [185] or/14 days [182]. | Inhibits Met signaling and helps to attenuate tumor spread/metastasis, independent of $H_2O_2$-related mechanisms [120]. 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 affectes the cell cycle of cancer cells via inhibiting of HES1 and Notch2 expressions [182]. Inhibit tumor growth and metastasis *in vivo* by upregulating the Nrf2-UGT1A signaling [185]. |
| | | EGCG + NaB | 10 μM E + (1,2,3,4,5 and 6 mM) N. $IC_{50}$: 10 μM E + 5 mM N | The combination treatment induces apoptosis and G2/M cell cycle arrest through decrease in HDAC1, DNMT1, survivin and HDAC activity [43]. |

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**Table 3** (*continued*)

| Cancers | Cell lines | EGCG Combination | Dose & $IC_{50}$ | 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]. |
| | SW480 | EGCG | 1, 10 and 50 μM [89]; 10,20 and 35 μg/mL [182] | 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 affectes the cell cycle of cancer cells via inhibiting of HES1 and Notch2 expressions [182]. |
| | | EGCG + Panaxadiol | E (0,10,20 and 30 μM) and/or P (0,10 and 20 μM) | Inhibit cell proliferation and induce cell cycle arrest [35]. |
| | | EGCG + EPA-FFA + GS | EGCG (0–175 μM) + EPA-FFA (0–150 μM) + GS extract (0–15 μM) for 24 h | 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 + 5-FU | 25–400 μM of EGCG and/or 2.5–40 μM 5-FU [37]. | EGCG enhances 5-FU sensitivity and induces apoptosis in 5-FU resistant cancer cells [37] |
| | SW620 | EGCG | 25,50,75 and 100 μg/mL | Inhibits 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]. |
| | LoVo | EGCG | 10,20 and 35 μg/mL | 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 (E) + Vitexin-2-O-xyloside (X) + Raphasatin (G) | E (10,20,30,40,50 μg/mL), × (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]. |
| | RKO | EGCG | 12.5,25,50 and 100 μM *in vitro*; 30 mg/kg IP injection to SCID male mice every other day for 2 weeks [118] | Inhibits cell proliferation and induces cell apoptosis through inhibition of Akt, activation and induction of p38 MAPK activation; inhibits liver metastasis *in vivo* and suppresses angiogenesis and induces apoptosis in liver metastasis [118]. |
| | | EGCG + NaB | 10 μM E + (1,2,3,4,5 and 6 mM) N. $IC_{50}$: 10 μM E + 5 mM N | The combination treatment induces apoptosis and G2/M cell cycle arrest through decrease in HDAC1, DNMT1, survivin and HDAC activity. Furthermore, p53-dependent induction of p21 and an increase in nuclear factor kappa B (NF-kB)-p65 [43]. |
| | – | EGCG-(poly[lactic-co-glycolic acid])-NPs | – | Modify DNA damage in human lymphocytes from colon cancer patients and healthy individuals treated *in vitro* with platinum-based chemotherapeutic drugs [187]. |
| **Glioma** | 1321N1 | EGCG | 50,100,150,200,250 and 300 μg/mL; $IC_{50}$: 82.0 ± 10.31 μg/mL (24 h) | Inhibits proliferation and induces apoptosis through activation of caspase-3 [30]. |
| | | EGCG + [6]-Gingerol | 50 μg/mL EGCG + GING; $IC_{50}$: 40 ± 8.62 μg/mL | Mixture inhibits proliferation and induces apoptosis through activation of caspase-3 [30]. |
| | | EGCG + Tocotrienol-rich fraction (TRF) | 100 μg/mL EGCG + TRF; $IC_{50}$: 100 ± 9.5 μg/mL | |
| | LN18 | EGCG | 50,100,150,200,250 and 300 μg/mL; $IC_{50}$: 134.0 ± 11.36 μg/mL (24 h) | Inhibits proliferation and induces apoptosis through activation of caspase-3 [30]. |
| | | EGCG + [6]-Gingerol | 50 μg/mL EGCG + GING; $IC_{50}$: 24 ± 2.65 μg/mL | Mixture inhibits proliferation and induces apoptosis through activation of caspase-3[30]. |
| | | EGCG + Tocotrienol-rich fraction (TRF) | 80 μg/mL EGCG + TRF; $IC_{50}$: 88 ± 11.14 μg/mL | |
| | SW1783 | EGCG | 50,100,150,200,250 and 300 μg/mL; $IC_{50}$: 300.0 ± 9.10 μg/mL (24 h) | Inhibits proliferation and induces apoptosis through activation of caspase-3 [30]. |
| | | EGCG + [6]-Gingerol | 60 μg/mL EGCG + GING; $IC_{50}$: 60 ± 5.6 μg/mL | Mixture inhibits proliferation and induces apoptosis through activation of caspase-3 [30]. |
| | | EGCG + Tocotrienol-rich fraction (TRF) | 100 μg/mL EGCG + TRF; $IC_{50}$: 270 ± 4.16 μg/mL | |
| | U87<br>U251<br>SHG-44<br>C6 | EGCG + Temozolomide | 100 μM E + 100 μM TMZ | EGCG inhibits properties of glioma stem-like cells ($CD133^{high}$/$ALDH1^{high}$) and synergizes with TMZ through downregulation of P-glycoprotein inhibition [42]. |

| | | | | |
|---|---|---|---|---|
| **Skin cancer** | A431 | EGCG | 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]. |
| | – | Green tea polyphenols | 200μL of a 5% solution | Prevent the adverse effects of UV radiation in humans [190]. |
| **Esophageal cancer** | TE-8 | EGCG | 40 μM *in vitro* | Reduces 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]. |
| | | EGCG (E) + Curcumin (C) | E (40 μmol/L), C (40 μmol/L), and L (4 μmol/L) *in vitro* | |
| | | EGCG (E) + Curcumin (C) + Lovastatin (L) | | |
| | SKGT-4 | EGCG | 40 μM *in vitro* and 50 μg/kg/d by oral intake into nude mice for 30 days (5 day/week) | |
| | | EGCG (E) + Curcumin (C) | E (40 μmol/L), C (40 μmol/L), and L (4 μmol/L) *in vitro* | |
| | | EGCG (E) + Curcumin (C) + Lovastatin (L) | | |
| **Adrenal cancer** | NCI-H295 | EGCG | 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 | EGCG | 10, 20, 40, 80 μg/mL | Inhibit cell adhesion, migration and invasion through downregulion of MMP-9 expression via blocking of NF-κB signaling pathway [121]. |
| | | EGCG (in green tea extract) + Ascorbic acid + Lysine + Proline + Arginine | 10,50,100,500 and 1000 μg/mL of the mixture | Mixture inhibits critical steps of cancer development and spread, such as MMP-2 and -9 secretions and invasion [137]. |
| **Pheochromocytoma** | PC-12 | EGCG | 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** | ($Nanog^{high}$/$Oct4^{high}$/$ATP7A^{low}$/$DKK2^{low}$)in BE(2)-C CSCs | EGCG | 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 | EGCG + HDHA-DOX-NPs | 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 anticancer activities of HDHA-NPs significantly increasing the mean survival time of the animals and inducing apoptosis [145]. |
| **Head and neck squamous carcinoma (HNSC) CSCs** | K3<br>K4<br>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, ABCC2, 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 chemo-drugs in CSCs, for instance, EGCG induces apoptosis through down-regulating 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-Pa-Ca-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 [128]. 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

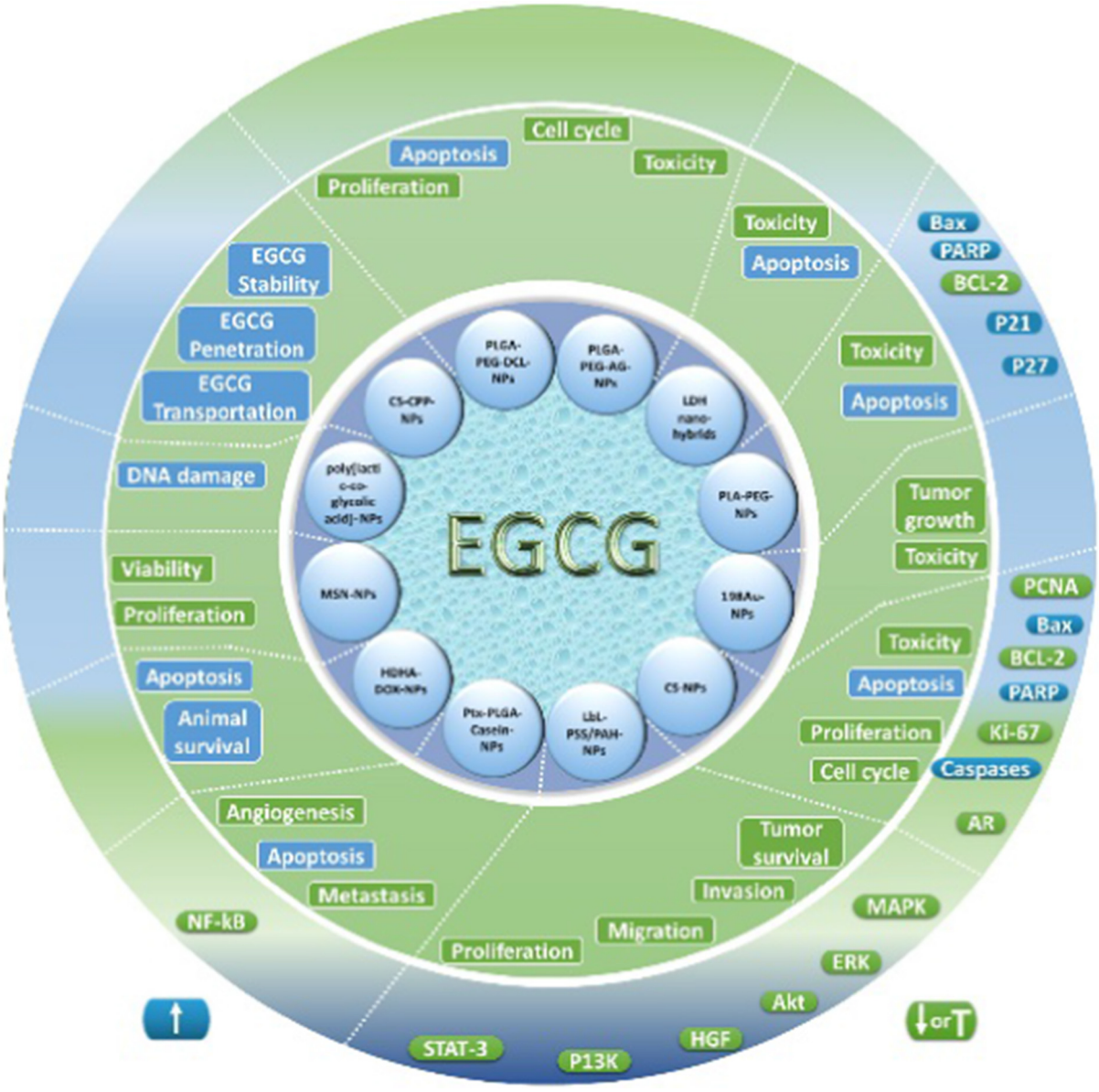


**Fig. 5.** Schematic drawing of the regulative actions of EGCG combined with nanoparticles. This carton is based on the available literature.

in almost complete inhibition of distant site metastases in prostate cancer. Furthermore, GTP consumption caused significant apoptosis of cancer cells causing inhibition of prostate cancer development, 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 BGC-823 cells were inhibited by a combination of EGCG and docetaxel [40] or a mixture of EGCG and capecitabine [38]. EGCG and ascorbic acid combination strongly suppressed proliferation 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 mixture inhibited critical steps of cancer development and spread, such as MMP-2 and -9 secretions and invasion in T-24 bladder cancer 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 Casp3/7, 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 nanoparticls

On the other hand, nanotechnology mediated approaches to develop drugs have attracted intense attention in cancer prevention and therapy research. Nanoparticles appears to hold great promise in the field of cancer management because of its unique physicochemical properties including nanometer size, large surface area-to-mass ratio, and efficient interaction with cells [2]. Siddiqui *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 demonstrated 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 cancer 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 expression with a concomitant decrease in Bcl-2 and activation of caspases [143]. Another study demonstrated apoptosis induction (Bax, PARP) in tumors harvested from the treated mice within 8-fold dose advantage of nanoformulation over native EGCG [144]. EGCG and HDHA-DOX-NPs combination induces apoptosis in Ehrlich'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 upregulating 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 regulatory 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 downregulated the key genes associated with angiogenesis, tumor metastasis and survival as well as induced apoptosis and inhibited NF-κB activation in MDA-MB-231 breast cancer cells [141].

## Conclusion

Chemoprevention, also defined as "slowing the process of carcinogenesis" concept appears to be a viable option for cancer control. 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 chemopreventive 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 belonging 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 polyphenols 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 chemopreventive agent. However, despite its beneficial therapeutic potential, 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 combination 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 pharmaceutical 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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