EGCG Epigallocatechin Gallate

Summary:
1. Concentration is a factor that could determine whether green tea polyphenols act as antioxidants or pro-oxidants
2. poor bioavailability: taking EGCG capsules without food was better
3. Cancer dosage 4g/day (2g twice per day)? with curcumin may help
4. EGCG is susceptible to oxidative degradation
5. “As for the pH level, the acidic environments enhance the stability of EGCG”
6. “EGCG may enhance nanoparticle uptake by tumor cells”
7. might be iron chelator (removing iron from cancer cells)
8. Claimed as synergistic effect with chemotherapy (cisplatin, bleomycin, gemcitabine
9. May suppress glucose metabolism, interfere with VEGF, downregulate NF-κB and MMP-9, down-regulation of androgen-regulated miRNA-21

https://pmc.ncbi.nlm.nih.gov/articles/PMC4739749/pdf/cureus-0007-000000000441.pdf

A Case of Complete and Durable Molecular Remission of Chronic Lymphocytic Leukemia Following Treatment with Epigallocatechin-3-gallate, an Extract of Green Tea 2015

Based on early-phase clinical trials showing the efficacy of epigallocatechin-3 gallate in chronic lymphocytic leukemia, author KB prescribed a supplement formula containing reishi mushroom (Ganoderma lucidum), chaga mushroom (Inonotus obliquus), and green tea (Camellia sinensis) [2]. This formulation was chosen because the green tea fraction provided approximately 1200 mg daily of epigallocatechin-3-gallate

To address these issues, the patient was placed on high-dose fish oil containing eicosapentaenoic acid (10.8 g) and docosahexaenoic acid (2.4 g daily), curcumin (4 g daily), vitamin D3, Scutellaria baicalensis, and probiotics. Calcium and magnesium were added to address a reported decrease in lumbar vertebral bone density.

In December 2010, author KB increased the dose of epigallocatechin-3-gallate to 4 g daily, basing the dose on that used in a clinical trial at Mayo Clinic [2]

In February 2011, two months after the patient began the higher dose of epigallocatechin-3-gallate, the white blood cell count peaked at 50,600/μL, with 84% lymphocytes. Fibrinogen, D-dimer, C-reactive protein, and C-peptide levels had dropped to low-optimal ranges. The vitamin D level had reached a supranormal level of 110 ng/dL, and the dose of supplemental vitamin D was decreased.

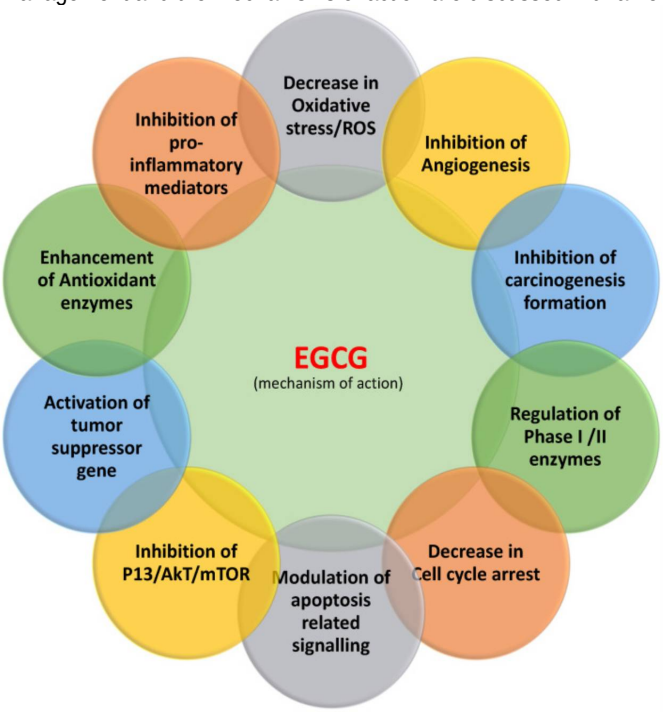
In 2015, more than three years after the documented remission, the patient remains well at age 52. He takes epigallocatechin-3-gallate (1200 mg) daily and maintains his self-directed lifestyle regimen.

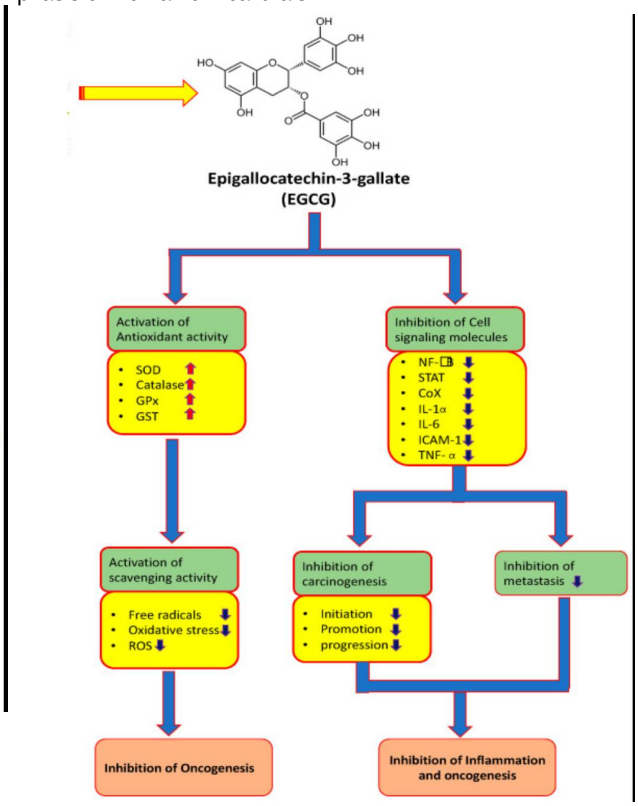
The timing of this second remission, shortly after an increase in dose of epigallocatechin-3-gallate to 4 g daily, is provocative, as is the concurrent use of curcumin. Preclinical studies show that epigallocatechin-3-gallate induces apoptosis in CLL B cells [2]. Whereas clinical trials have found epigallocatechin-3-gallate alone active against chronic lymphocytic leukemia, preclinical work suggests curcumin may potentiate the antitumor effect [2,8

https://pubmed.ncbi.nlm.nih.gov/32660101/

Potential Therapeutic Targets of Epigallocatechin Gallate (EGCG), the Most Abundant Catechin in Green Tea, and Its Role in the Therapy of Various Types of Cancer 2020

EGCG has been proven to possess a chemopreventive effect through inhibition of carcinogenesis process such as initiation, promotion, and progression. In addition, this catechin has proven its role in cancer management through modulating various cell signaling pathways such as regulating proliferation, apoptosis, angiogenesis and killing of various types of cancer cells. The additive or synergistic effect of epigallocatechin with chemopreventive agents has been verified as it reduces the toxicities and enhances the anti-cancerous effects. Despite its effectiveness and safety, the implications of EGCG in cancer prevention is certainly still discussed due to a poor bioavailability. Several studies have shown the ability to overcome poor bioavailability through nanotechnology-based strategies such as encapsulation, liposome, micelles, nanoparticles and various other formulation. In this review, we encapsulate therapeutic implication of EGCG in cancer management and the mechanisms of action are discussed with an emphasis on human clinical trials.





https://pmc.ncbi.nlm.nih.gov/articles/PMC11478201/

Immunomodulatory Effects of Green Tea Catechins and Their Ring Fission Metabolites in a Tumor Microenvironment Perspective 2024

Studies using rats showed that less than 5% of catechins from an orally administered dose of tea reach the bloodstream [5,14].

In humans, the highest levels of catechin plasma concentrations appeared to occur 1–2.5 h after intake. EGCG has a longer half-life (~5 h) than EGC and EC (~3 h), contrasting with its limited bioavailability [16].

The hallmarks of cancer are characterized by several key features, including continuous cell division, ability to evade immune destruction, resistance to cell death, ability to replicate indefinitely, stimulation of blood vessel growth (angiogenesis), activation of invasion and metastasis, alteration of energy metabolism, and ability to evade mechanisms that typically restrict cell proliferation [52]. EGCG has been demonstrated to target multiple cancer hallmarks in various types of cancer [50].

Lowe et al. demonstrated higher leukocyte activation in healthy people when supplemented with 300 mg of GTE for 14 days. Although the leukocyte count was not influenced by supplementation, there was an increased secretion of myeloperoxidase and lactoferrin, molecules that activate mature neutrophils and monocytes [94].

https://pubmed.ncbi.nlm.nih.gov/23201840/

Epigallocatechin Gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea 2012

In this study, we determined the cancer chemopreventive potentials of 10 representative polyphenols (caffeic acid, CA; gallic acid, GA; catechin, C; epicatechin, EC; gallocatechin, GC; catechin gallate, CG; gallocatechin gallate, GCG; epicatechin gallate, ECG; epigallocatechin, EGC; and epigallocatechin gallate, EGCG), and explored their structure-activity relationship. The effect of the 10 polyphenol compounds on the proliferation of HCT-116 and SW-480 human colorectal cancer cells was evaluated using an MTS assay. Cell cycle distribution and apoptotic effects were analyzed by flow cytometry after staining with propidium iodide (PI)/RNase or annexin V/PI. Among the 10 polyphenols, EGCG showed the most potent antiproliferative effects, and significantly induced cell cycle arrest in the G1 phase and cell apoptosis.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3679539/

Antioxidant effects of green tea 2013

Green tea polyphenols are believed to be responsible for this cancer preventive effect, and the antioxidant activity of the green tea polyphenols has been implicated as a potential mechanism.

Green tea polyphenols can also be potent pro-oxidants, both *in vitro* and *in vivo*, leading to the formation of hydrogen peroxide, the hydroxyl radical, and superoxide anion. The potential role of these pro-oxidant effects in the cancer preventive activity of green tea is not well understood. The evidence for not only the antioxidant, but also pro-oxidant, properties of green tea are discussed in the present review.

Adding milk to green tea decreases formation of hydrogen peroxide, independent of the presence of catalase [8], which decomposes hydrogen peroxide into water and oxygen. It could be that the polyphenols in green tea bind to proteins in milk, thereby inhibiting hydrogen peroxide production. Under oxidative conditions polymerization of green tea polyphenols can also occur [9].

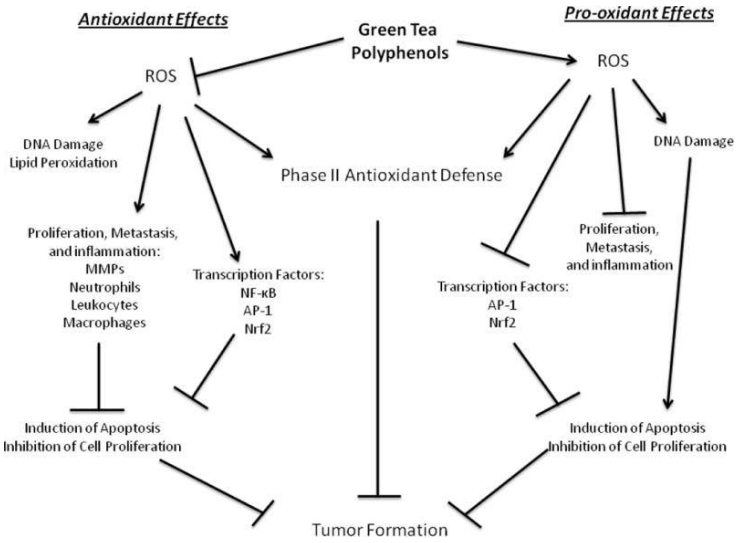
Selenium could enhance anticancer activity of green tea [29], possibly by enhancing antioxidant activity [30, 31], or even its pro-oxidant activity [32].

The basis for anticancer properties of green tea polyphenols *in vitro* and *in vivo* could due to their antioxidant or pro-oxidant properties (Fig 2). Due to conflicting evidence, it is likely that the specific oxidative mechanism depends on the type of cancer and environment surrounding cancer cells.

Green tea polyphenols accelerate pro-oxidant reactions depending on experimental conditions. EPR has shown that all green tea polyphenols can undergo auto-oxidation at alkaline (pH 13) conditions, which leads to oxidation of the B ring [35]. Similar oxidative reactions have also been shown to occur at physiological pH (7.4) [70]. When EGCG and EGC are reacted with H_2O_2, the A ring of both compounds become oxidized followed by decarboxylation to form two oxidation products of EGCG and one oxidation product of EGC [71]. This is a pro-oxidant effect as such reactions produce the hydroxyl radical in the presence of iron or copper (Fenton).

Concentration is a factor that could determine whether green tea polyphenols act as antioxidants or pro-oxidants *in vitro*. EGC and EGCG, both generate hydrogen peroxide at concentrations greater than 10 μM [85]. This was shown in lymphoblastoid cell lines, where both EGCG and ascorbic acid at levels of 1 to 10 μM offered DNA protection against bleomycin, yet the protective effects were lost at 100 μM [86].

Evidence also exists for a potential pro-oxidant basis for the anti-cancer effects of tea polyphenols *in vivo*. H_2O_2 was generated in the oral cavity of human subjects by either holding green tea in the mouth or chewing green tea leaves. The production of H_2O_2 was directly proportional to the concentration of green tea polyphenols in the mouth, and has implications for oral cancer prevention [90].



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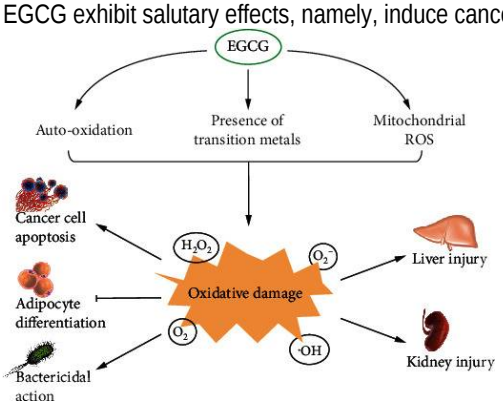
Prooxidant Effects of Epigallocatechin-3-Gallate in Health Benefits and Potential Adverse Effect 2020

Epigallocatechin-3-gallate (EGCG) is the major polyphenolic compound present in green tea and is generally regarded as an effective antioxidant. However, its chemical reactivity makes it susceptible to generate reactive oxygen species (ROS) via autooxidation and exhibit prooxidant effects. The prooxidant actions of

EGCG could play a dual role, being both beneficial and harmful. This review summarized recent research progress on (1) the anticancer, antiobesity, and antibacterial effects of EGCG and (2) the possible toxicity of EGCG. The major focus is on the involvement of prooxidant effects of EGCG and their effective doses used. Considering dosage is a crucial factor in the prooxidant effects of EGCG; further studies are required to find the appropriate dose at which EGCG could bring more health benefits with lower toxicity.
The prooxidant effects of EGCG were thought to be potential mechanisms for anticancer action. The anticancer mechanisms varied depending on the cell type, dose, and/or time of treatment (Table 1) [18–36].
Considering the cytotoxicity of EGCG in normal cells, the IC_{50} value in normal cells was checked and showed to be more than 200 μM, while that for the corresponding cancer cells was 132 μM [25]. These results suggested that cancer cells are more sensitive to EGCG than normal cells, and ROS might be selectively toxic to cancer cells.
In a safety study on EGCG, the genetic, acute, and short-term toxicity was examined, and a no-observed adverse effect level (NOAEL) of 500 mg/kg/day EGCG was established [73].
EGCG has a variety of beneficial functions, which could be attributed to its antioxidant properties. However, EGCG could also function as a prooxidant under certain conditions (Figure 6). Its prooxidant effects into the cells were evidenced as oxidative damage to the cell structures, including DNA and lipids. This oxidative damage results from excess ROS produced by EGCG. Several approaches have been proposed to explain how EGCG induces the production of a mass of ROS. They include autooxidation processes of EGCG, presence of transition metals, and mitochondrial ROS. On the one hand, the prooxidant effects of EGCG exhibit salutary effects, namely, induce cancer cell apoptosis, inhibit adipocyte differentiation, and cause bactericidal action.



https://pmc.ncbi.nlm.nih.gov/articles/PMC3909779/
New insights into the mechanisms of polyphenols beyond antioxidant properties; lessons from the green tea polyphenol, epigallocatechin 3-gallate 2014
However, treatment of cells with EGCG results in production of hydrogen peroxide and hydroxyl radicals in the presence of Fe (III). Thus, EGCG functions as a pro-oxidant in some cellular contexts.
Highlights
- •Many biological actions of EGCG are mediated by specific mechanisms other than its well-known anti-oxidant properties.
- •EGCG is a pro-oxidant per se in some biological contexts.
- •EGCG directly interacts with cell surface membrane proteins and specific known receptors.
- •Treatment of cells with EGCG regulates specific intracellular signaling pathways and transcription.
- •Specific biological actions of EGCG are regulated in a concentration-dependent manner.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8706847/
Simple Approach to Enhance Green Tea Epigallocatechin Gallate Stability in Aqueous Solutions and Bioavailability: Experimental and Theoretical Characterizations 2021
It is well known that EGCG degradation in aqueous solutions mainly proceeds through oxidation and autoxidation involving several factors, among which the most influencing are pH, light, heat, dissolved oxygen, and metal ions [13,14,15,16].
Citric acid was used to fix the pH of the oral solution to 3.5–4.5, a range optimal for EGCG stability.
Besides, as metal ions may catalyze EGCG degradation, the presence of citric acid is also meant to scavenge these potential trace impurities by formation of complexes. Glucose was used as a reducing sugar and a radical scavenger.
Composition of the solution.

	Percentage Formula (% w/w)
EGCG	2.68
Citric acid	0.05
Glucose	23.4
Sucrose	10.0
Cola flavor	0.6
Water for injection	ad 100%

EGCG in two doses of 400 mg per day in most cases, which, according to our formulation, would provide 7 g glucose and 3 g sucrose.

Indeed, according to the available data [8,29], the stability of EGCG in water at 37 °C depends on the concentration, but can hardly exceed a half-life of 4 h [8,29].

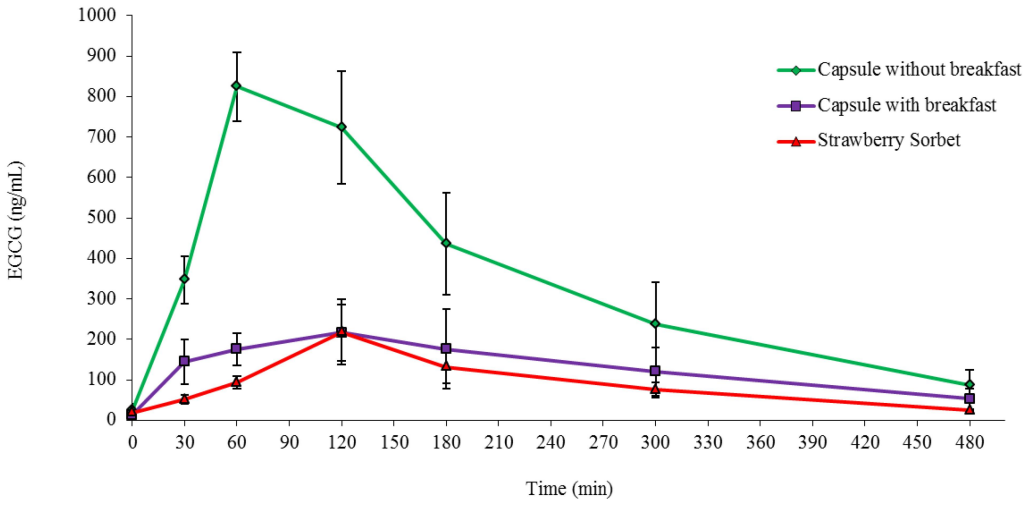
From the formulator's point of view, the EGCG challenge is highly complicated. Indeed, its high antioxidant properties make it particularly **susceptible to oxidative degradation**, which requires consideration of pH [6], reducing oxygen content during the manufacturing process and in the finished product [7], adding antioxidant agents while knowing that most of them are less reducing than EGCG and thus offer only low protection, and keeping metal ions (iron, zinc, copper, aluminum) as low as possible [8].

https://pmc.ncbi.nlm.nih.gov/articles/PMC6225204/
The Effect of Ultrasound, Oxygen and Sunlight on the Stability of (−)-Epigallocatechin Gallate 2018
We found that the stability of EGCG was concentration-dependent in water at room temperature. Both sunlight and oxygen influenced the stability of EGCG, and

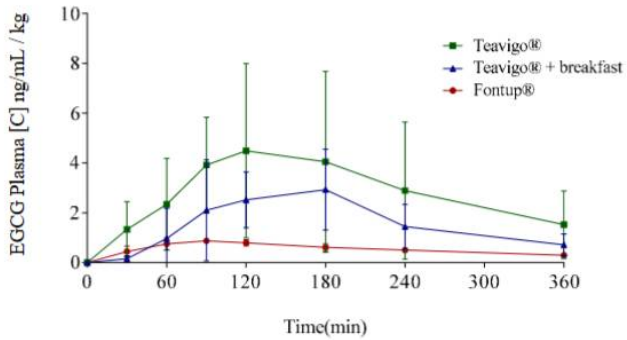
oxygen had a more pronounced effect on stability of EGCG than sunlight. The most important conclusion was that the ultrasound may accelerate the degradation of EGCG due to the presence of oxygen and sunlight, but not because of the ultrasonic vibration.
Aqueous EGCG solution is highly unstable, as EGCG can easily degrade through oxidation and epimerization [10,11]. The rates of these two reactions are affected by many factors, such as the presence of oxygen or sunlight, as well as changes of temperature, pH and ionic strength [9,12,13].
As for the pH level, the acidic environments enhance the stability of EGCG, but neutral and alkaline pH level cause auto-oxidation on the B-ring and produce theasinensin A and product P2 [17,18].
Without oxygen, EGCG in aqueous solution was rather stable,

https://pubmed.ncbi.nlm.nih.gov/15284381/
Piperine enhances the bioavailability of the tea polyphenol (-)-epigallocatechin-3-gallate in mice 2004
Here, we report that cotreatment with a second dietary component, piperine (from black pepper), enhanced the bioavailability of EGCG in mice.

https://www.mdpi.com/2076-3921/4/2/373
Food Inhibits the Oral Bioavailability of the Major Green Tea Antioxidant Epigallocatechin Gallate in Humans 2015
The bioavailability of the most abundant and most active green tea antioxidant, epigallocatechin gallate (EGCG) remains uncertain. Therefore, the systemic absorption of EGCG was tested in healthy fasted humans. It was administered as capsules with water or with a light breakfast, or when incorporated within a strawberry sorbet. The results for plasma EGCG clearly revealed that taking EGCG capsules without food was better; the AUC was 2.7 and 3.9 times higher than when EGCG capsules were taken with a light breakfast ($p = 0.044$) or with EGCG imbedded in the strawberry sorbet ($p = 0.019$), respectively.
after an overnight fast of at least 10 h, the participants ingested 500 mg of EGCG given either as two capsules (2 × 250 mg) with 100 mL of water only .... and no additional food was taken for a further 4 h.



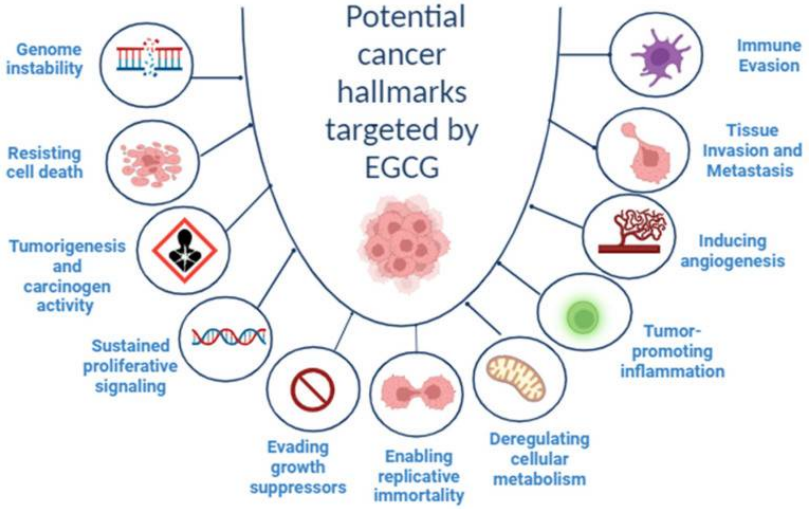
https://www.researchgate.net/publication/341598633_Bioavailability_of_Epigallocatechin_Gallate_Administered_With_Different_Nutritional_Strategies_in_Healthy_Volunteers
Bioavailability of Epigallocatechin Gallate Administered With Different Nutritional Strategies in Healthy Volunteers 2020



The present study shows a higher bioavailability for the Teavigo® intake with no additional food compared to the other two preparations tested taken either with food or with a dietetic supplement.
EGCG has been administered in the form of green tea extract (Teavigo®), in a single dose of 250 mg after overnight fasting, showing significant differences according to the conditions and nutritional supplements used [23].
For that, the green tea extract should be ingested alone after overnight fasting to optimize the gastrointestinal absorption of the EGCG. These results are consistent with previous studies in which the authors proposed that the administration of EGCG alone elicits an attenuated strong response from the stomach and pancreas, minimizing the digestion processes [17, 57]. When a capsule containing EGCG with no additional food is ingested after fasting overnight and arrives to the stomach, the gastrointestinal processes are only partially activated just by that small amount of nutrients. Then, the EGCG molecules remain stable due to the propitious acidic environment (pH < 3) , where the **oxidation** of their polar residues is minimized [58]. In addition, the neutralization process by the secretion of bile salts is not activated, which favors and increases their absorption by the enterocytes in the small intestine.

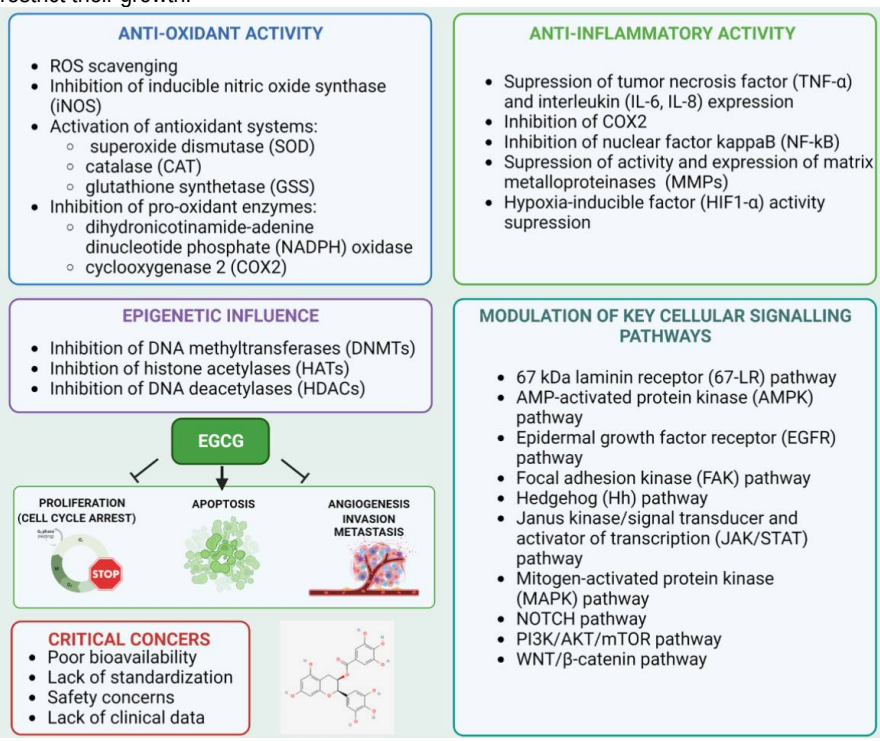
https://pmc.ncbi.nlm.nih.gov/articles/PMC10976257/
Targeting Cancer Hallmarks with Epigallocatechin Gallate (EGCG): Mechanistic Basis and Therapeutic Targets 2024
EGCG anticancer activity is mediated by interfering with various cancer hallmarks. This article summarize and highlight the effects of EGCG on cancer hallmarks

and focused on the impacts of EGCG on these cancer-related hallmarks.



One of the main reasons behind the low bioavailability of EGCG is intestinal metabolism. Intestinal metabolism affects the bioavailability of flavonoids. It was shown that EGCG was easily metabolized by *Raoultella planticola*, *Enterobacter aerogenes* (*Klebsiella planticola*), *Bifidobacterium longum* subsp., and *K. pneumoniae* subsp. [20]. These types of bacteria are found frequently in gut microbiota [20].
One of the practices that is utilized to increase EGCG bioavailability is using other natural products such as curcumin and piperine. Curcumin was reported to inhibit P-glycoprotein pump, thus inhibiting EGCG efflux [22], while with piperine, coadministration of EGCG and piperine as 163.8 micromole/kg and 70.2 micromole/kg to male CF-1 mice enhanced the area under the curve and maximum plasma concentration by 1.3-fold related to mice treated with EGCG alone [23].

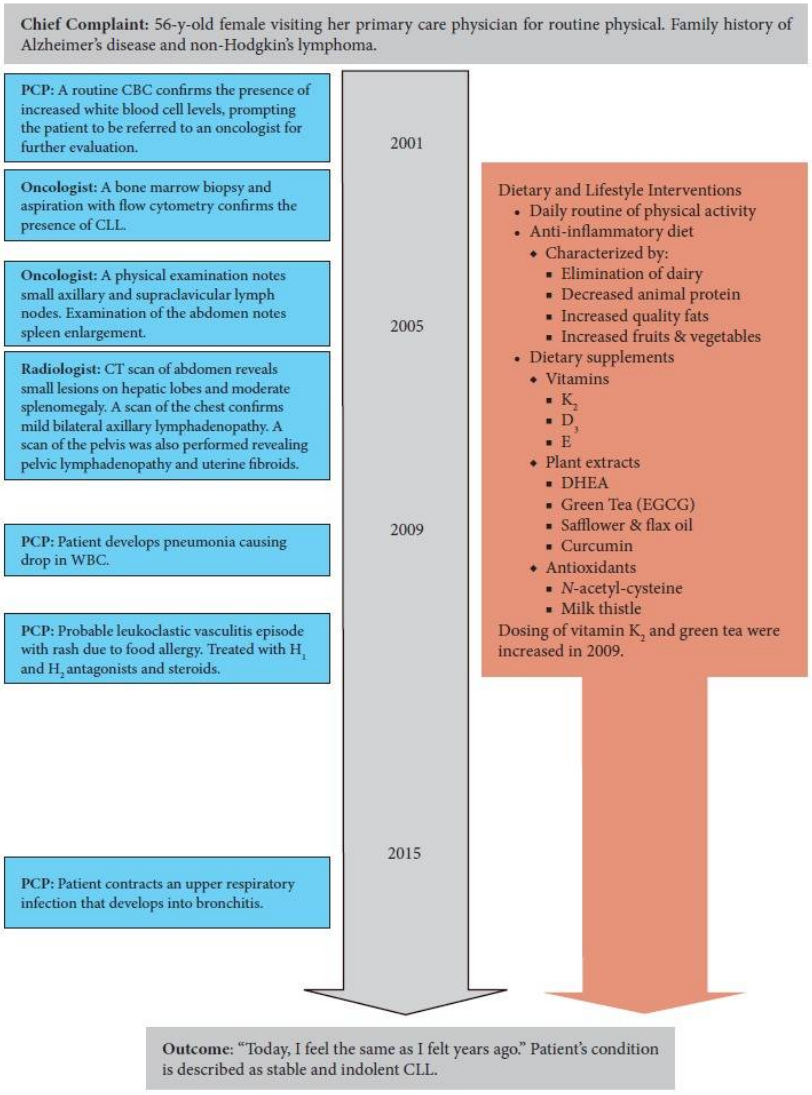
https://pmc.ncbi.nlm.nih.gov/articles/PMC10343677/pdf/molecules-28-05246.pdf
Epigallocatechin-3-Gallate Therapeutic Potential in Cancer: Mechanism of Action and Clinical Implications 2023
It was discovered that the combined practice of drinking green tea and taking a bath in hot springs resulted in a higher concentration of EGCG in the plasma [379
The understanding of the molecular mechanisms of the anticancer activity of this compound revealed the versatile capability of this catechin to influence multiple pivotal signaling pathways inside the cell including, but not limited to, EGFR, JAK/STAT, PI3K/AKT/mTOR, and MAPK. EGCG has been found to modulate epigenetic mechanisms such as DNA methylation and histone modifications by targeting epigenetic modulators such as DNMTs, HATs, and HDACs (Figure 6). Moreover, new emerging targets of EGCG have been identified. For example, EGCG acts as an ATP-competitive inhibitor of GRP78, a chaperone protein that promotes chemoresistance and inhibits apoptosis in cancer cells. EGCG has been found to suppress GRP78 activity and hinder its expression, particularly in glioblastomas. EGCG has been identified as a compound with a significant capability of HK2 inhibition. HK2 plays a role in the metabolic shift towards aerobic glycolysis in cancer cells. EGCG effectively suppresses ZAP-70 activity, a protein tyrosine kinase involved in the signaling process mediated by T-cell receptors. Through reverse docking methodology and network pharmacology, EGCG has been found to impact multiple signaling pathways and proteins. These include FYN, NOS2, CDK2, ABL1, SYK, AKT1/2, MAPK8, IRAK4, and APAF1, which have been previously investigated in in vitro studies. Additionally, novel targets including IKKβ, KRAS, NTRK1, and WEE1 have been identified. EGCG has shown a moderate suppression of WEE1 activity and an efficient inhibition of IKKβ, KRAS, and NTRK1 in enzymatic assays. Future studies may also elucidate new mechanisms through which EGCG may suppress the development of tumors or restrict their growth.



Despite the initial enthusiasm for EGCG use in cancer treatment, conflicting epidemiological data were obtained considering EGCG consumption and the decreased risk of many cancers. No clear evidence suggests that tea consumption reduces the overall risk of developing cancer.
Furthermore, the clinical use of EGCG is hindered by its poor oral bioavailability, low intestinal absorption, and short retention time. Overcoming these challenges is necessary for its widespread use in clinical settings.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6380985/

Case Report of Unexpectedly Long Survival of Patient With Chronic Lymphocytic Leukemia: Why Integrative Methods Matter 2018



Abbreviations: PCP, primary care provider; CBC, complete blood count; CLL, chronic lymphocytic leukemia; CT, computed tomography; WBC, white blood count; DHEA; dehydroepiandrosterone; EGCG, epigallocatechin-3-gallate.

Chronic lymphocytic leukemia (CLL)

A clinical trial found EGCG to be effective against CLL.[31] Preclinical research on EGCG, the active ingredient in green tea, suggests that it may interfere with vascular endothelial growth factor (VEGF) receptors in these cells.[21,22] CLL cells are characterized by their resistance to apoptosis, which is believed to be maintained by the secretion and binding of VEGF. There is also preclinical evidence indicating that curcumin may potentiate the effects of EGCG on CLL.[26,32,33] The patient consumed 1000 mg of curcumin phytosome daily. Furthermore, results from a clinical trial on Rai stage 0/1 CLL patients suggests these patients may benefit from curcumin therapy.[33]

The patient's maximum WBC reached 175 000; however, it stabilized and later began to slowly decrease, possibly plateauing in the 120 000 to 130 000 range after high-dose epigallocatechin-3-gallate (EGCG) was added to her diet and supplements regimen.

During this period, the patient also began a physician-assisted regimen of alternative dietary supplements. The complete list of supplements included the following: **vitamin K_2**; mixed **omega-3/omega-6** oil; **vitamin D_3**; meriva-500 (**curcumin**); combination of **milk thistle** and **broccoli** extract; ***N*-acetyl-cysteine, methylation** support product combining methyl-B_{12}, **methylfolate, riboflavin, vitamin B_6, and trimethylglycin**; high-potency **multivitamin** with activated B **vitamins, mixed tocopherols, and carotenoids; low-dose dehydroepiandrosterone;** and **high-dose EGCG green tea extract (equivalent of approximately 1800 mg of EGCG per day).**

A clinical trial found **EGCG to be effective against CLL**.[31] Preclinical research on EGCG, the active ingredient in green tea, suggests that it may interfere with vascular endothelial growth factor (VEGF) receptors in these cells.[21,22] CLL cells are characterized by their resistance to apoptosis, which is believed to be maintained by the secretion and binding of VEGF. There is also preclinical evidence indicating that curcumin may potentiate the effects of EGCG on CLL.[26,32,33] The patient consumed 1000 mg of curcumin phytosome daily. Furthermore, results from a clinical trial on Rai stage 0/1 CLL patients suggests these patients may benefit from curcumin therapy.[33]

https://pmc.ncbi.nlm.nih.gov/articles/PMC3902473/

Phase 2 Trial of Daily, Oral Polyphenon E in Patients with Asymptomatic, Rai Stage 0-II Chronic Lymphocytic Leukemia(CLL) 2012

Previously untreated patients with asymptomatic, Rai stage 0-II CLL and an absolute lymphocyte count(ALC) ≥10 ×10^9/L were eligible for this phase II trial. Polyphenon E with a standardized dose of epigallocatechin-3-gallate(2000 mg per dose) was administered twice daily.

Overall, 29(69%) patients fulfilled the criteria for a biologic response with either a sustained ≥20% decline in ALC and/or a ≥30% reduction in the sum of the products of all nodal areas at some point during the 6 months of active treatment.

Green tea has long been promoted as a health promoting substance which reduces the risk of cancer.[1, 2] After 3 case-control studies demonstrated that green tea

intake was associated with a reduced risk of leukemia[3, 4] and non-Hodgkin lymphoma[5], a population based cohort study of ~42,000 individuals prospectively followed for 9 years was conducted.[6] Green tea consumption was inversely associated with the risk of lymphoid malignancies even after adjusting for 16 other personal characteristics including age, sex, smoking history, level of education, occupation, consumption of other dietary products, and family history of leukemia.[6]
Polyphenon E capsules containing ~200 mg of EGCG were supplied by the NCI or directly by Polyphenon E International(PEI). All patients in the Phase II portion of the trial received Polyphenon E at a dose of 1000 mg orally twice per day for the first 7 days of cycle 1 at which point they increased the dose to 2000 mg orally twice per day. Polyphenon E was administered with a light meal/snack.
One patient treated at the phase II dose level of the phase I trial achieved a partial remission according to the NCI working group criteria. Most (67%) patients had a reduction in ALC(Table 3; Figure 2A) which was transient in some patients while others had a steady, sustained stepwise reduction throughout the 6 months of active therapy.
While spontaneous regressions occasionally occur in patients with CLL, such remissions are rare(~1% in most series[32-34]).

https://www.sciencedirect.com/science/article/abs/pii/S0304885322009453
Characterization of mesenchymal stem cells with augmented internalization of magnetic nanoparticles: The implication of therapeutic potential 2022
Highlights
•An effective strategy to **augment uptake of magnetic nanoparticles by mesenchymal stem cells was established using epigallocatechin gallate in the magnetic field.**
• Mesenchymal stem cells with such treatment retained characteristics of stemness or differentiation.
•The findings may set up a foundation of a platform for using mesenchymal stem cells in theranostic application.
Epigallocatechin gallate (EGCG) has been known to greatly enhance MNP uptake by tumor cells under the influence of magnetic fields. However, whether EGCG significantly improves the MNP uptake by MSCs in the magnetic fields and whether MSCs maintain the characteristics of MSCs with such treatment remains unknown. In this study, we demonstrated that EGCG significantly enhanced the MNP uptake by MSCs in the magnetic field. With 30 μM EGCG in the magnetic field for 2 h, the cell-associated MNPs are increased 7.1 and 3.4 times by mouse and human MSCs without a distinguished influence on cell morphology, respectively.

https://www.nature.com/articles/cddis2017563
A new molecular mechanism underlying the EGCG-mediated autophagic modulation of AFP in HepG2 cells 2017
Our results suggest that EGCG is critical in regulating AFP secretion and in modulating autophagic activities of $HepG_2$ cells, providing a molecular basis for potentially preventing and treating HCC.
In addition, a novel method combined anti-AFP-coated magnetic Fe_3O_4 nanoparticles with **low-frequency electromagnetic field** exposure induced the apoptosis of Bel-7402 and $HepG_2$ hepatoma cells lines without manifesting any significant side effects on HL-7702, a normal hepatic cell line.[18] Notably, EGCG could inhibit AFP secretion in human hepatoma-derived PLC/PRF/5 cells[19] and reduces the serum AFP level in HCC rat models.[20] However, the mechanism underlying the way by which EGCG regulates AFP levels in HCC cells remains elusive. By using a combined approach with both experimental and computational techniques, we aim to demonstrate the effect of EGCG on AFP secretion, and more importantly, to reveal the underlying relationship between AFP secretion and EGCG-induced autophagic activities in human HCC $HepG_2$ cells.

https://pubmed.ncbi.nlm.nih.gov/27186307/
Effects of combined delivery of extremely low frequency electromagnetic field and magnetic Fe3O4 nanoparticles on hepatic cell lines 2016
Magnetic Fe3O4 nanoparticles (MNPs) have shown promise as drug carriers for treating lung and liver tumors in vivo. However, little is known about the combined delivery of these MNPs with a second approach, extremely low frequency electro-magnetic field (ELFF) exposure, which has been shown to have value for in vitro treatment of tumor cells. Here, ELFF and MNPs were combined to treat healthy (HL-7702) and cancerous (Bel-7402, HepG2) hepatic cells lines to explore the potential therapeutic effects, bio-mechanisms, and potential toxicity of a combined drug-free treatment in vitro. Flow cytometry for anti-AFP (alpha fetal protein) antibody, which coated the MNPs, indicated that the combined treatment induced Bel-7402 and HepG2 hepatoma cells lines into early apoptosis, without significant effects on healthy hepatic cells. This effect appeared to be mediated through cellular membrane ion metabolism. The presence of AFP-loaded MNPs strengthened the effects of ELFF on tumor cells, inducing a higher frequency of early apoptosis, while having minimal toxic effects on healthy HL-7702 cells. Western blotting revealed that the apoptosis-triggering BCL proteins were up regulated in hepatoma cells compared to healthy cells. Flow cytometry and patch-clamp studies revealed that this resulted from a higher MNP uptake ratio and greater cellular membrane ion exchange current in tumor cells compared to HL-7702 cells. Further, patch-clamp results showed that combining MNPs with ELFF treatment induces cells into early apoptosis through an ion metabolism disturbance in cells, similar to ELFF treatment. In brief, the combination of ELFF and MNPs had beneficial effects on tumor cells without significant toxicity on healthy cells, and these effects were associated with cellular MNP uptake.

https://www.researchgate.net/publication/323871065_Interaction_of_poly-l-lysine_coating_and_heparan_sulfate_proteoglycan_on_magnetic_nanoparticle_uptake_by_tumor_cells
Interaction of poly-l-lysine coating and heparan sulfate proteoglycan on magnetic nanoparticle uptake by tumor cells 2018
In addition to PLL, research has indicated that epigallocatechin-3-gallate (EGCG), a polyphenolic component in tea, enhances MNP internalization,38 which is also negatively charged due to the presence of phenolic groups. Moreover, EGCG is a known antioxidant with antitumor and anti-inflammatory activities,39–41 which are probably mediated by interaction with a 67 kDa laminin receptor.
Unlike PLL, EGCG and magnetic force exerted a synergistic effect on MNP internalization by U87MG cells, as illustrated in Figure 3D. At 10 μM EGCG, the magnetic force increased MNP cell by 3.1-fold, suggesting that the enhancing effect of EGCG is very sensitive to magnetic fields. Similar effects of EGCG have also been observed in LN229 cells.3
However, it is noticeable that the magnetic field and EGCG had a remarkably synergistic effect on enhancing MNP internalization by both U87MG and LN229 cells.

https://pubmed.ncbi.nlm.nih.gov/35893779/
Laminin Receptor-Mediated Nanoparticle Uptake by Tumor Cells: Interplay of Epigallocatechin Gallate and Magnetic Force at Nano-Bio Interface 2022
Epigallocatechin gallate (EGCG), a major tea catechin, enhances cellular uptake of magnetic nanoparticles (MNPs), but the mechanism remains unclear. EGCG induced a concentration-dependent enhancement effect of MNP internalization by LN-229 glioma cells, which was synergistically enhanced by the application of a magnetic field. Transmission electron microscopy demonstrated that EGCG increased the number, but not the size, of internalized vesicles, whereas EGCG and the magnet synergistically increased the size of vesicles.

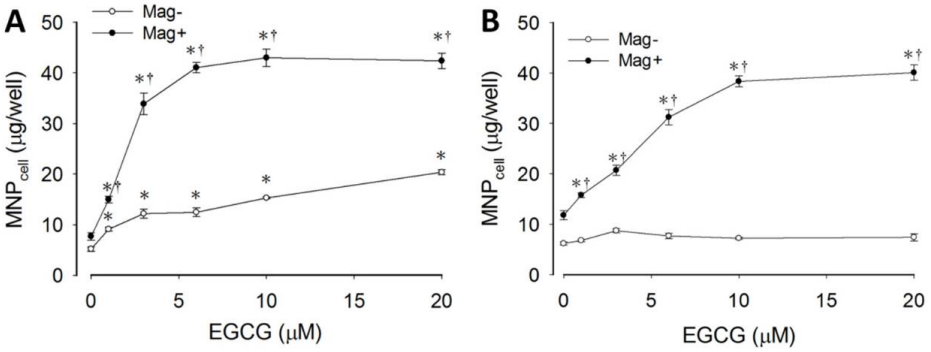


Figure 1. EGCG-enhanced uptake of MNPs by tumor cells. LN-229 (**A**) and A431 (**B**) cells were incubated with CMX-MNPs (50 µg/well) in the absence (Mag−) or presence (Mag+) of the magnet for 2 h prior to determination of cell-associated MNPs (MNP_{cell}). Values are mean ± SEM ($n = 4$). *, † $p < 0.05$ compared with corresponding group without EGCG or magnet, respectively.

https://pubmed.ncbi.nlm.nih.gov/25069428/

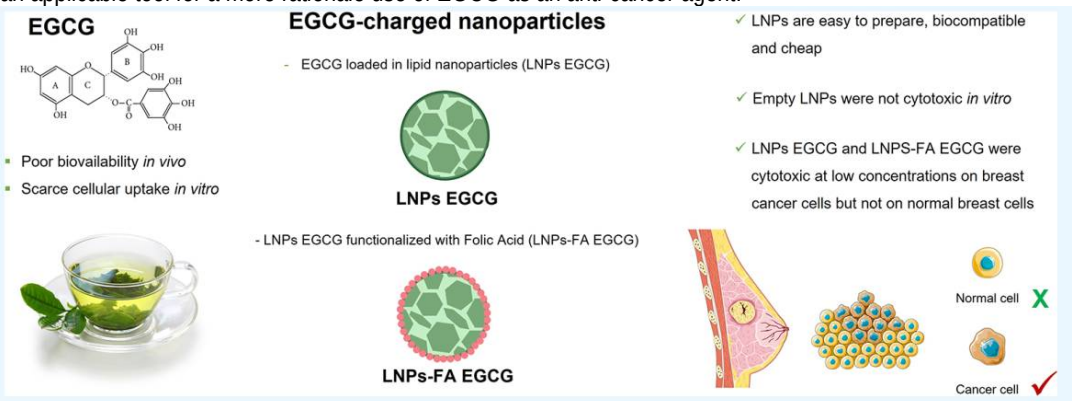
Augmented cellular uptake of nanoparticles using tea catechins: effect of surface modification on nanoparticle-cell interaction 2014

Nanoparticles may serve as carriers in targeted therapeutics; interaction of the nanoparticles with a biological system may determine their targeting effects and therapeutic efficacy. Epigallocatechin-3-gallate (EGCG), a major component of tea catechins, has been conjugated with nanoparticles and tested as an anticancer agent. We investigated whether EGCG may enhance nanoparticle uptake by tumor cells. Cellular uptake of a dextran-coated magnetic nanoparticle (MNP) was determined by confocal microscopy, flow cytometry or a potassium thiocyanate colorimetric method. We demonstrated that EGCG greatly enhanced interaction and/or internalization of MNPs (with or without polyethylene glycol) by glioma cells, but not vascular endothelial cells. The enhancing effects are both time- and concentration-dependent. Such effects may be induced by a simple mix of MNPs with EGCG at a concentration as low as 1-3 µM, which increased MNP uptake 2- to 7-fold. In addition, application of magnetic force further potentiated MNP uptake, suggesting a synergetic effect of EGCG and magnetic force. Because the effects of EGCG were preserved at 4 °C, but not when EGCG was removed from the culture medium prior to addition of MNPs, a direct interaction of EGCG and MNPs was implicated. Use of an MNP-EGCG composite produced by adsorption of EGCG and magnetic separation also led to an enhanced uptake.

https://pubs.acs.org/doi/10.1021/acsomega.2c01829

Epigallocatechin-3-gallate Delivered in Nanoparticles Increases Cytotoxicity in Three Breast Carcinoma Cell Lines 2022

The anticancer activity of epigallocatechin-3-gallate (EGCG), orally administrated, is limited by poor bioavailability, absorption, and unpredictable distribution in human tissues. EGCG charged nanoparticles may represent an opportunity to overcome these limitations. We assayed two different kinds of lipid nanoparticles (LNPs and LNPs functionalized with folic acid) charged with EGCG on three breast carcinoma cell lines (MCF-7, MDA-MB-231, and MCF-7TAM) and the human normal MCF10A mammary epithelial cells. Both LNPs loaded with EGCG, at low concentrations, induced a significant cytotoxicity in the three breast carcinoma cells but not in MCF10A cells. In view of a future application, both LNPs and LNPs-FA were found to be very suitable for *in vitro* studies and useful to improve EGCG administration *in vivo*. Since they are produced by inexpensive procedures using bioavailable, biocompatible, and biodegradable molecules, they represent an applicable tool for a more rationale use of EGCG as an anti-cancer agent.



The sizes of the LNPs used in this study were 333 and 313 nm in the case of nonfunctionalized and functionalized LPNs...
The LNPs were produced by highshear homogenization and ultra-sonication techniques.
For the production of EGCG-loaded LNPs, EGCG was dissolved in the aqueous phase and added to the lipid phase in a similar manner to previously described.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7559993/

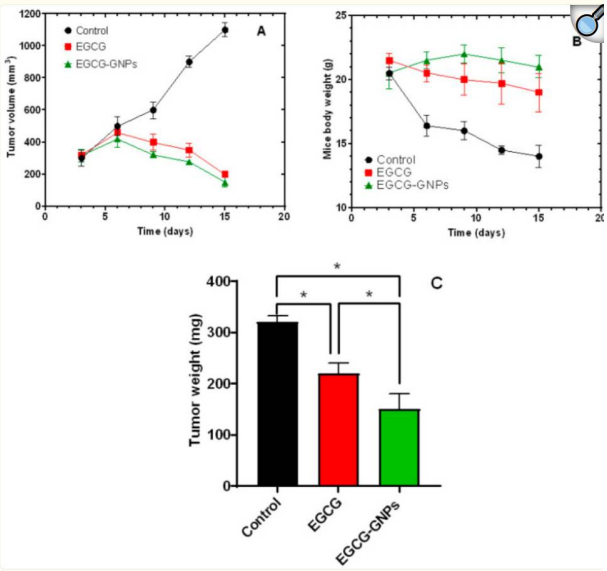
Epigallocatechin-3-Gallate-Loaded Gold Nanoparticles: Preparation and Evaluation of Anticancer Efficacy in Ehrlich Tumor-Bearing Mice 2020

To enhance EGCG anticancer efficacy, it was loaded onto gold nanoparticles (GNPs). EGCG-GNPs were prepared by a simple green synthesis method and were evaluated using different techniques.
The particle size ranged from ~26 to 610 nm.

2.1. Preparation of EGCG-GNPs

A green synthesis approach was used for the preparation of EGCG-loaded GNPs where HAuCl4 was reduced in aqueous solution using EGCG. This approach is eco-friendly, clean, simple, efficient, and avoids the use of hazardous man-made chemicals [25,32]. EGCG has eight orthophenolic hydroxyl groups, which form complexes with Au3+ ions and facilitate their reduction to gold ions to form EGCG-capped GNPs [25]. In addition to acting as a reducing agent, EGCG could also serve as a stabilizing agent for GNPs due to the acidity of EGCG phenolic groups, which results in negative charge at pH 7.4 [25]. The color of the EGCG and HAuCl4 mixture changed from pale yellow to purple red within 15 min due to surface plasmon resonance (SPR) phenomenon confirming the formation of gold nanoparticles [34]. Further evidence of the formation of EGCG-GNPs was ascertained from TEM measurements (Figure 1), which shows EGCG-GNPs (formulation F2) as discrete, spherical particles with no aggregation. The size obtained from TEM measurements was 13.6 ± 5.1 nm. This particle size is smaller than that obtained by dynamic light scattering (DLS) measurements (33.8 ± 2.2 nm, Table 1). This is a commonly observed behavior for nanoparticles due to the

dry status of nanoparticles used in TEM measurements, which probably results in nanoparticle shrinkage. In contrast, the size obtained by DLS represents hydrated nanoparticles in solution, which explains their bigger size [35,36].



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(**A**) Ehrlich ascites carcinoma growth curve. (**B**) Changes in the body weight of the Ehrlich tumor-bearing mice as a function of time. (**C**) Weight of the tumor at the end of the study. * Statistically significant difference ($p < 0.05$). The observed results confirm that loading of EGCG onto GNPs resulted in significant enhancement of its anticancer efficacy.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7645157/

Advanced Nanovehicles-Enabled Delivery Systems of Epigallocatechin Gallate for Cancer Therapy 2020

The construction of EGCG-loaded nanovehicles has been generally recognized to enhance the stability and bioavailability of EGCG, exhibiting great potential for practical applications in cancer chemoprevention and chemotherapy. Numerous nanomaterials, including gold nanoparticles, mesoporous silica nanostructures, chitosan nanoparticles, lipid nanoparticles, and protein nanoassemblies, can serve as carriers for delivering EGCG to tumor tissues, while the delivery efficiency is highly dependent on the morphological and surface characteristics of nanovehicles (Figure 1).

https://www.semanticscholar.org/paper/EGCG-coated-silver-nanoparticles-self-assemble-with-Yang-Wang/36ea7fc4cf689f9c6637599e8374ae35fdaef86f

EGCG-coated silver nanoparticles self-assemble with selenium nanowires for treatment of drug-resistant bacterial infections by generating ROS and disrupting biofilms 2022

In this work, we successfully synthesized a safe and effective antibacterial nano-formulation of Se@Ag@EGCG by self-assembly of epigallocatechin gallate (EGCG)-coated silver nanoparticles (Ag) on the surface of selenium nanowires (Se). The in vitro bacteriostatic results showed that 40 μg ml−1 Se@Ag@EGCG had significant antibacterial activity against drug-resistant Staphylococcus aureus (S. aureus) and Escherichia coli (E. coli) by destroying the formation of bacterial biofilm, promoting the production of high concentration reactive oxygen species and destroying bacterial cell wall. In addition, the results of in vivo antibacterial experiments showed that subcutaneous administration of 10 mg kg−1 of Se@Ag@EGCG could promote wound healing by reducing apoptosis and inflammatory responses in infected wounds. It is worth mentioning that the reduced and modified Se@Ag@EGCG by this natural product has negligible in vivo toxicity. This development strategy of nano-antibacterial materials, which breaks through the drug resistance mechanism, provides new ideas for the development of drugs for drug-resistant bacterial infections.

https://link.springer.com/article/10.1007/s00449-013-1094-0

Epigallocatechin-3-gallate-capped Ag nanoparticles: preparation and characterization 2013

We used an aqueous leaf extract of *Camellia sinensis* to synthesize Ag nanoparticles (AgNPs). A layer of ca. 6 nm around a group of the AgNPs in which the inner layer is bound to the AgNPs surface via the hydroxyl groups of catechin has been observed.

https://www.nature.com/articles/s41598-020-62136-2

Anticancer effects of epigallocatechin-3-gallate nanoemulsion on lung cancer cells through the activation of AMP-activated protein kinase signaling pathway 2020

Epigallocatechin-3-gallate (EGCG), a green tea–derived polyphenol, exhibits antitumor activities. An EGCG nanoemulsion (nano-EGCG) was prepared to improve the stability and reduce the side effects of EGCG for treatment of human lung cancer cells, and the antitumor effects were studied. The possible molecular mechanism underlying its antitumor effects on cultured human lung cancer cells was also elucidated.

Our results showed that both EGCG and nano-EGCG inhibited the growth of H1299 lung cancer cells, with half-maximal inhibitory concentrations of 36.03 and 4.71 μM, respectively. Additionally, nano-EGCG effectively suppressed lung cancer cell colony formation, migration, and invasion in a dose-dependent manner. Nano-EGCG may inhibit lung cancer cell invasion through matrix metalloproteinase (MMP)-2- and MMP-9-independent mechanisms. Furthermore, the expression of several key regulatory proteins in the AMPK signaling pathway was modulated by nano-EGCG. Nano-EGCG may inhibit lung cancer cell proliferation, colony formation, migration, and invasion through the activation of AMPK signaling pathways. This novel mechanism of nano-EGCG suggests its application in lung cancer prevention and treatment.

https://www.researchgate.net/publication/347873100_The_Role_of_EGCG_in_Breast_Cancer_Prevention_and_Therapy
The Role of EGCG in Breast Cancer Prevention and Therapy 2020
EGCG shows antioxidant or pro-oxidant properties, depending on the concentration and exposure time. EGCG blocks cell cycle progression and modulates signaling pathways that affects cell proliferation and differentiation. EGCG also induces apoptosis, negatively modulates different steps involved in metastasis and targets angiogenesis by inhibiting VEGF transcription. In vivo, investigations have shown that oral administration of EGCG results in reduction of tumor growth and in antimetastatic and antiangiogenic effects in animal xenograft and allograft models. Discussion Much remains unknown about the molecular mechanisms involved in the protective effects of EGCG on mammary carcinogenesis. In addition, more studies in vivo are necessary to determine the potential toxicity of EGCG at higher doses and to elucidate its interactions with other drugs. Conclusion A protective effect of EGCG has been shown in different experimental models and under different experimental conditions, suggesting clinical implications of EGCG for breast cancer prevention and therapy.

https://www.researchgate.net/publication/318469094_Anti-cancer_effect_of_EGCG_and_its_mechanisms
Anti-cancer effect of EGCG and its mechanisms 2016
For example, 67-kDa laminin receptor (67LR) was recently identified as the sensing molecule for EGCG. 67LR overexpresses in cancer cells and plays a crucial role in the selective toxicity of EGCG.
The 67-kD laminin receptor (67LR), also known as Ribosomal Protein SA (RPSA), is a cell surface receptor for laminin with high affinity [17]. This receptor is peculiar, as only a full length gene encoding a 37-kDa precursor protein of 295-amino acids has been isolated. 67LR is involved in adhesion in normal cells, however, several pathological studies suggested the 67LR has been shown to be overexpressed in various types of cancer including breast cancer [17, 18], pancreatic cancer [18], gastric cancer [18], chronic lymphocytic leukemia [19], melanoma [8], multiple myeloma [9, 10], and acute myelogenous leukemia [20]. Our finding revealed that 67LR could be an attractive target for cancer chemotherapy and provide a rationale for the clinical value of EGCG as a 67LR-targeting drug.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10341956/
The Potential Role of Epigallocatechin-3-Gallate (EGCG) in Breast Cancer Treatment 2023
EGCG has shown multiple effects on the major signaling pathways governing carcinogenesis and cancer progression, including MAP kinase (MAPK), phosphatidylinositol-3 kinase (PI3K), nuclear factor κB (NFkB), and reducing the increased levels of phosphorylation of ERK1/2 and Jak/STAT3 [14]. In addition, it acts by modulating the receptors typically expressed in breast cancer, such as ER and ErbB [15,16,17].
EGCG inhibits the expression of epidermal growth factor receptors (EGFR or ErbB) such as ErbB1 and ErbB2, which are overexpressed in breast cancer [19], especially in epidermoid carcinoma (A-431) and SK-BR3.
EGCG interfered with glycolytic processes, decreasing the expression of key enzymes involved in the regulation of glucose metabolism and lactate production, such as phosphofructokinase (PFK), lactate dehydrogenase (LDH), and hexokinase (HK), as well as the glucose transporter GLUT1, producing lower glucose consumption, lactate production, and ATP generated by metabolism [49]. EGCG also inhibited the expression of hypoxia-inducible factor 1α (HIF1α), which is overexpressed in tumors [50].

https://cancerci.biomedcentral.com/articles/10.1186/s12935-023-03081-8
Epigallocatechin-3-gallate and cancer: focus on the role of microRNAs 2023
MicroRNAs (miRNAs) are a group of small non-coding RNAs that affect gene expression. The role of miRNAs in different types of cancers has been published and it was shown that several miRNAs are inappropriately expressed in different cancers.
Recent research shows that phytochemicals, including epigallocatechin-3-gallate (EGCG), exert important epigenetic-based anticancer effects such as pro-apoptotic or anti proliferative through miRNA gene silencing. Given that EGCG is able to modulate a variety of cancer-related process i.e., angiogenesis, proliferation, metastasis and apoptosis via targeting various miRNAs such as let-7, miR-16, and miR-210. The discovery of new miRNAs and the differences observed in their expression when exposed to EGCG provides evidence that targeting these miRNAs may be beneficial as a form of treatment

https://cancerci.biomedcentral.com/articles/10.1186/s12935-023-03161-9
Epigallocatechin-3-gallate and its nanoformulation in cervical cancer therapy: the role of genes, MicroRNA and DNA methylation patterns 2023
Further research on cervical cancer has revealed the crucial role of epigenetic mechanisms in the initiation and progression of this type of cancer. These include changes to the DNA, histones, and non-coding RNAs, such as microRNAs. These changes are reversible and can occur even before genetic mutations, making them a potential target for intervention therapies. One promising approach to cancer prevention and treatment is the use of specific agents (known as **epi-drugs**) that target the cancer epigenome or epigenetic dysregulation. Phytochemicals, a group of diverse molecules, have shown potential in modulating cancer processes through their interaction with the epigenetic machinery. Among these, green tea and its main polyphenol EGCG have been extensively studied. This review highlights the therapeutic effects of EGCG and its nanoformulations on cervical cancer.

https://www.researchgate.net/publication/341133182_The_Epigenetic_Modification_of_Epigallocatechin_Gallate_EGCG_on_Cancer
The Epigenetic Modification of Epigallocatechin Gallate (EGCG) on Cancer 2020
Another mechanism that explains the multiple effects exerted by EGCG in cancer is the epigenetic change by DNA methylation or methyltransferases, histone acetylation or deacetylases, and no coding RNAs (micoRNAs).

https://pmc.ncbi.nlm.nih.gov/articles/PMC6315581/
Molecular Targets of Epigallocatechin—Gallate (EGCG): A Special Focus on Signal Transduction and Cancer 2018
EGCG interacts with DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), which modulates epigenetic changes.

https://www.researchgate.net/publication/340088640_Iron_Chelation_Properties_of_Green_Tea_Epigallocatechin-3-Gallate_EGCG_in_Colorectal_Cancer_Cells_Analysis_on_TfrFth_Regulations_and_Molecular_Docking
Iron Chelation Properties of Green Tea Epigallocatechin-3-Gallate (EGCG) in Colorectal Cancer Cells: Analysis on Tfr/Fth Regulations and Molecular Docking 2020
In many studies, green tea epigallocatechin-3-gallate (EGCG) has already shown its therapeutic effects in colorectal cancer cells (CRC). However, its mechanism of actions in CRC is poorly elucidated.
The strong interaction predicted between EGCG to ferritin may lead to inhibition of ferritin by EGCG, thus supporting the downregulation of FtH observed in in vitro studies. Molecular docking study of TfR to EGCG cannot be modulated based on the in vitro results. In conclusion, EGCG possesses iron chelator property in CRC and this potential could be further exploited for CRC treatment.
However, excessive iron is very likeable by cancer cells as these irons lead to cancer progression. Thus, it is very important to remove these excessive irons from the cancer cells so that the tumor-related progression can be stunted with the lack or absence of iron [11, 12].

In this experiment, the treatment of EGCG had caused TfR being upregulated and FtH being down-regulated, indicating that iron chelation activity had occurred in the HT-29.

https://www.researchgate.net/publication/282316276_Biocompatible_and_biodegradable_nanoparticles_for_enhancement_of_anti-cancer_activities_of_phytochemicals

Biocompatible and biodegradable nanoparticles for enhancement of anti-cancer activities of phytochemicals 2015

Many phytochemicals show promise in cancer prevention and treatment, but their low aqueous solubility, poor stability, unfavorable bioavailability, and low target specificity make administering them at therapeutic doses unrealistic. This is particularly true for **(-)-epigallocatechin gallate**, curcumin, quercetin, resveratrol, and genistein. There is an increasing interest in developing novel delivery strategies for these natural products. Liposomes, micelles, nanoemulsions, solid lipid nanoparticles, nanostructured lipid carriers and poly (lactide-co-glycolide) nanoparticles are biocompatible and biodegradable nanoparticles. Those nanoparticles can increase the stability and solubility of phytochemicals, exhibit a sustained release property, enhance their absorption and bioavailability, protect them from premature enzymatic degradation or metabolism, prolong their circulation time, improve their target specificity to cancer cells or tumors via passive or targeted delivery, lower toxicity or side-effects to normal cells or tissues through preventing them from prematurely interacting with the biological environment, and enhance anti-cancer activities.

https://www.researchgate.net/publication/362395636_When_Natural_Compounds_Meet_Nanotechnology_Nature-Inspired_Nanomedicines_for_Cancer_Immunotherapy

When Natural Compounds Meet Nanotechnology: Nature-Inspired Nanomedicines for Cancer Immunotherapy 2022

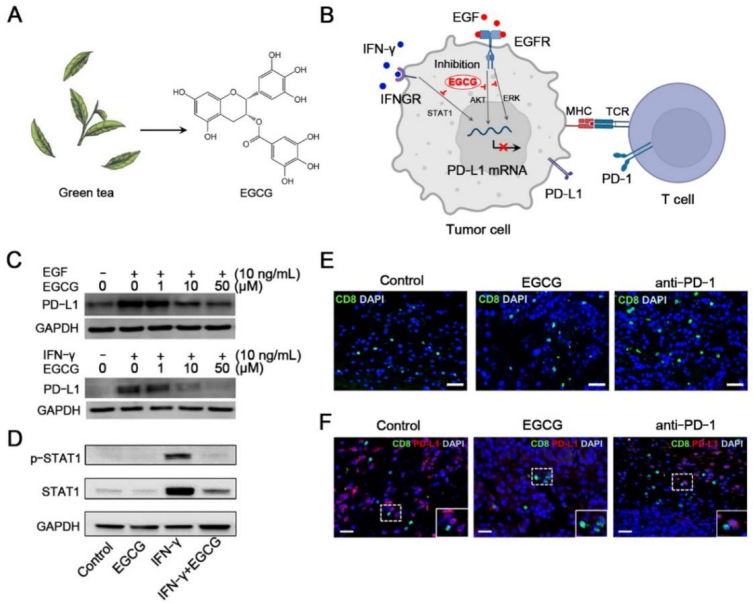


Figure 3. Schematic of EGCG for cancer immunotherapy. (**A**) EGCG is the active compound derived from green tea. (**B**) Schematic of the mechanisms of EGCG for the inhibition of the PD-1/PD-L1 axis. (**C**) Downregulation of epidermal growth factor (EGF) and IFN-γ-induced PD-L1 protein in Lu99 cells after EGCG treatment. (**D**) Downregulation of p-STAT1 and STAT1 in B16F10 cells after EGCG treatment. (**E**) Immunofluorescence images of tumor tissue sections stained with CD8 (green)

https://www.researchgate.net/publication/360934968_The_Potential_of_Epigallocatechin_Gallate_EGCG_in_Targeting_Autophagy_for_Cancer_Treatment_A_Narrative_Review

The Potential of Epigallocatechin Gallate (EGCG) in Targeting Autophagy for Cancer Treatment: A Narrative Review 2022

Reviewed articles reveal that EGCG promotes cytotoxic autophagy often through the inactivation of PI3K/Akt/mTOR pathway, resulting in apoptosis induction. EGCG pro-oxidant activity has been postulated to be responsible for its anti-cancer effects. In combination therapy with a chemotherapy drug, EGCG inhibits cell growth and the drug-induced pro-survival autophagy. The selected studies rightly claim EGCG as a valuable agent in cancer chemoprevention.

https://www.researchgate.net/publication/338109917_Induction_of_Endoplasmic_Reticulum_Stress_Pathway_by_Green_Tea_Epigallocatechin-3-Gallate_EGCG_in_Colorectal_Cancer_Cells_Activation_of_PERKp-eIF2_a_ATF4_and_IRE1_a

Induction of Endoplasmic Reticulum Stress Pathway by Green Tea Epigallocatechin-3-Gallate (EGCG) in Colorectal Cancer Cells: Activation of PERK/p-eIF2 α /ATF4 and IRE1 α 2019

This study was aimed to determine the mechanism of actions of EGCG when targeting the endoplasmic reticulum (ER) stress pathway in CRC

https://pmc.ncbi.nlm.nih.gov/articles/PMC5824026/

Cancer Prevention with Green Tea and Its Principal Constituent, EGCG: from Early Investigations to Current Focus on Human Cancer Stem Cells 2018

The first part of this review summarizes ground-breaking topics with EGCG and green tea extract:
1) Delayed cancer onset as revealed by a 10-year prospective cohort study,
2) Prevention of colorectal adenoma recurrence by a double-blind randomized clinical phase II trial,
3) Inhibition of metastasis of B16 melanoma cells to the lungs of mice,
4) Increase in the average value of Young's moduli, i.e., cell stiffness, for human lung cancer cell lines and inhibition of cell motility and
5) Synergistic enhancement of anticancer activity against human cancer cell lines with the combination of EGCG and anticancer compounds.

In the second part, we became interested in cancer stem cells (CSCs). 1) Cancer stem cells in mouse skin carcinogenesis by way of introduction, after which we discuss two subjects from our review on human CSCs reported by other investigators gathered from a search of PubMed, 2) Expression of stemness markers of human CSCs compared with their parental cells, and 3) EGCG decreases or increases the expression of mRNA and protein in human CSCs. On this point, EGCG inhibited self-renewal and expression of pluripotency-maintaining transcription factors in human CSCs.

https://www.researchgate.net/publication/304940512_Epigallocatechin-3-gallate_targets_cancer_stem-like_cells_and_enhances_5-fluorouracil_chemosensitivity_in_colorectal_cancer

Epigallocatechin-3-gallate targets cancer stem-like cells and enhances 5-fluorouracil chemosensitivity in colorectal cancer 2016

A small subset of cancer cells, termed "cancer stem cells" (CSCs), are believed to be key contributors of chemoresistance and tumor recurrence. Recently, epigallocatechin-3-gallate (EGCG), an active catechin present in green tea, has been shown to suppress CSC growth in various cancers, but whether it can specifically target CSCs and subsequently sensitize chemoresistant CRC cells to standard of care chemotherapeutic treatments remains unknown.

Collectively our data provide novel and previously unrecognized evidence for EGCG-induced sensitization to 5FU through targeting of CSCs in CRC. Our data highlight that in addition to its chemopreventive ability, EGCG may serve as an adjunctive treatment to conventional chemotherapeutic drugs in CRC patients.

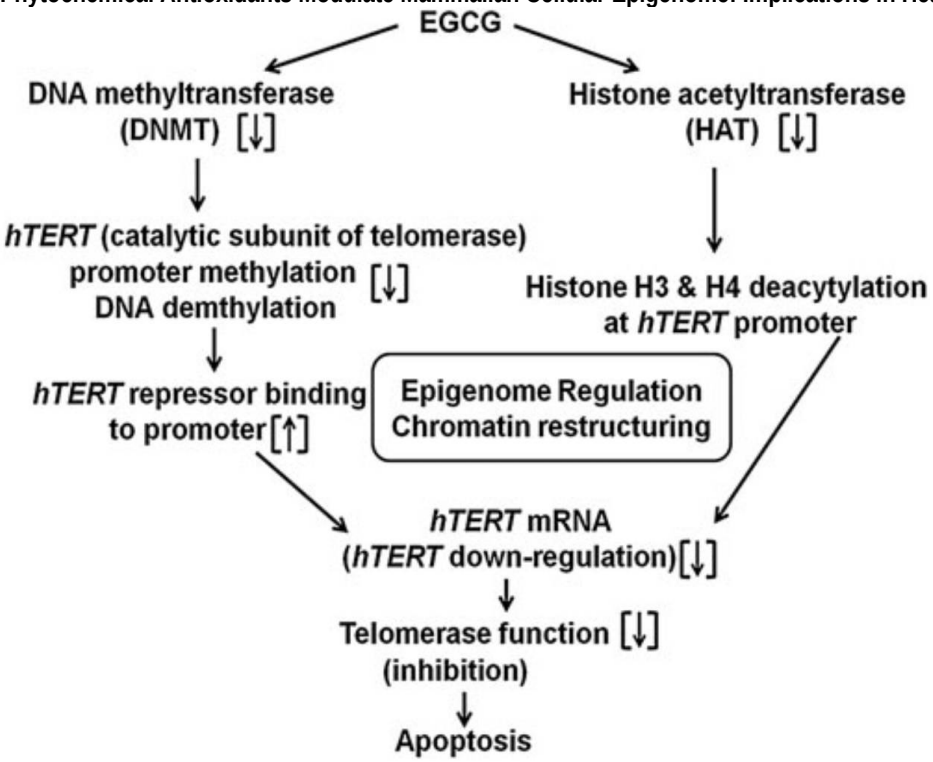
https://www.researchgate.net/publication/321911600_Cancer_preventive_and_therapeutic_effects_of_EGCG_the_major_polyphenol_in_green_tea

Cancer preventive and therapeutic effects of EGCG, the major polyphenol in green tea 2018

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

https://www.researchgate.net/publication/221690592_Phytochemical_Antioxidants_Modulate_Mammalian_Cellular_Epigenome_Implications_in_Health_and_Disease

Phytochemical Antioxidants Modulate Mammalian Cellular Epigenome: Implications in Health and Disease 2012



Mechanism of EGCG-induced apoptosis in cancer cells through epigenetic regulation of telomerase. According to Berletch et al. (11) and Meeran et al. (52), EGCG inhibits both deoxyribonucleic acid (DNA) methyltransferase (DNMT) and histone acetyltransferase (HAT), leading to the DNA demethylation and histones H3 and H4 deacetylation of the human telomerase-reverse transcriptase (hTERT) promoter, respectively. These events result in the epigenome regulation and chromatin restructuring involving hTERT messenger ribonucleic acid (mRNA) downregulation and inhibition of telomerase and ultimately cancer cell death (apoptosis). However, these studies have not provided any links between the antioxidant actions of EGCG and its epigenetic regulation of apoptosis of the cancer cells.

https://www.researchgate.net/publication/366419122_The_applications_of_epigallocatechin_gallate_EGCG-nanogold_conjugate_in_cancer_therapy

The applications of epigallocatechin gallate (EGCG)-nanogold conjugate in cancer therapy 2023

The current review focuses on the nanogold-based carriers containing EGCG, with an emphasis on the chemotherapeutic effects of EGCG in cancer treatment. The nanoscale vehicle may improve the EGCG solubility and bioavailability while overcoming constraints and cellular barriers.

https://www.researchgate.net/publication/328236054_Suppressing_glucose_metabolism_with_epigallocatechin-3-gallate_EGCG_reduces_breast_cancer_cell_growth_in_preclinical_models

Suppressing glucose metabolism with epigallocatechin-3-gallate (EGCG) reduces breast cancer cell growth in preclinical models 2018

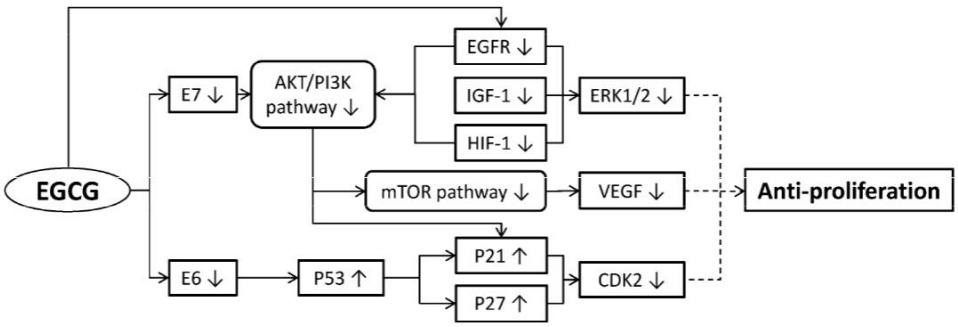
This study investigated the capacity of EGCG to suppress breast cancer cell growth in vitro and in vivo, characterizing the underlying mechanisms, focusing on the effect of EGCG on glucose metabolism.

In conclusion, EGCG exerts an anti-tumor effect through the inhibition of key enzymes that participate in the glycolytic pathway and the suppression of glucose metabolism.

https://www.researchgate.net/publication/327610816_Suppressive_Effects_of_EGCG_on_Cervical_Cancer

Suppressive Effects of EGCG on Cervical Cancer 2018

As a natural product, (-)-epigallocatechingallate (EGCG) has abilities in anti-proliferation, anti-metastasis and pro-apoptosis of cervical cancer cells. Moreover, EGCG also has pharmaceutical synergistic effects with conventional agents such as cisplatin (CDDP) and bleomycin (BLM).



https://www.researchgate.net/publication/250926581_Targeting_the_AMP-Activated_Protein_Kinase_for_Cancer_Prevention_and_Therapy

Targeting the AMP-Activated Protein Kinase for Cancer Prevention and Therapy 2013

Among the latest developments is the activation of AMPK by naturally occurring dietary constituents and plant products - termed phytochemicals. Owing to their efficacy and safety, phytochemicals are considered as an alternative to the conventional harmful chemotherapy. The rising popularity of using phytochemicals for cancer prevention and therapy is supported by a substantial progress in identifying the molecular pathways involved, including AMPK.

Recently, AMPK was found to be a new molecular target of curcumin (Figure 2).

Quercetin Induces apoptosis via AMPK activation and p53 in HT-29 colon cancer cells (88)

Resveratrol Induces apoptosis in chemoresistant HT-29 colon cancer cells via modulation of AMPK signaling pathway(74

Berberine Inhibits colon cancer migration via AMPK activation-mediated downregulation of integrin signaling (100)

Epigallocatechin gallate (EGCG) EGCG analogs activate AMPK, leading in inhibition of cell proliferation, up-regulation of the cyclin-dependent kinase inhibitor p21, downregulation of the mTOR pathway, and suppression of stem cell population in human breast cancer cells (96

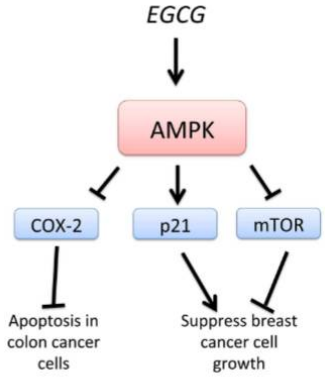


FIGURE 5 | Schematic representation of AMPK-dependent anti-cancer effects of EGCG. Epigallocatechin-3-gallate, EGCG, stimulates AMPK, leading to suppression of breast cancer cell growth by inhibition of mTOR and activation of p21. Inhibition of COX-2 by EGCG-induced AMPK activation leads to apoptosis in colon cancer cells.

https://www.researchgate.net/publication/370713821_Improving_the_anti-tumor_effect_of_EGCG_in_colorectal_cancer_cells_by_blocking_EGCG-induced_YAP_activation

Improving the anti-tumor effect of EGCG in colorectal cancer cells by blocking EGCG-induced YAP activation 2023

The anti-tumor effects of EGCG stem from its ability to inhibit the activities of many oncoproteins, such as AKT, VEGFR, STAT3, and mutant p53. However, the clinical efficacy of EGCG is unsatisfactory. How to improve the anti-tumor effects of EGCG is an open question. Here we report that EGCG inhibits the tumor suppressive Hippo signaling pathway and activates downstream YAP in colorectal cancer (CRC) cells. Activation of YAP impedes the anti-tumor effects of EGCG. YAP blockade increases the sensitivity of CRC cells to EGCG treatment.

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https://www.researchgate.net/publication/339583519_The_Big_Five_Phytochemicals_Targeting_Cancer_Stem_Cells_Curcumin_EGCG_Sulforaphane_Resveratrol_and_Genistein

The “Big Five” Phytochemicals Targeting Cancer Stem Cells: Curcumin, EGCG, Sulforaphane, Resveratrol and Genistein 2020

Certain phytochemicals, in particular curcumin, epigallocatechin-3-gallate (EGCG), sulforaphane, resveratrol and genistein have been shown to interfere with these intrinsic CSC pathways in vitro and in human xenograft mice, leading to elimination of CSCs. Moreover, recent clinical trials have demonstrated therapeutic efficacy of the five phytochemicals, alone or in combination with modern cancer therapeutics, and in various types of cancer. Since current cancer therapies fail to eradicate CSCs, leading to cancer recurrence and progression, targeting of CSCs with phytotochemicals such as curcumin, EGCG, sulforaphane, resveratrol and genistein, combined with each other and/or in combination with conventional cytotoxic drugs and novel cancer therapeutics, may offer a novel therapeutic strategy against cancer.

https://www.researchgate.net/publication/287947721_Prevention_effect_of_EGCG_in_rat's_lung_cancer_induced_by_benzopyrene

Prevention effect of EGCG in rat's lung cancer induced by benzopyrene 2012

CONCLUSIONS: EGCG has prevention effect in rats lung cancer induced by benzopyrene. It may associate with the inhibition of NF-κB p50 and Ki-67's expression.

https://www.researchgate.net/publication/289992020_Estrogen_receptor-a36_is_involved_in_epigallocatechin-3-gallate_induced_growth_inhibition_of_ER-negative_breast_cancer_stemprogenitor_cells

Estrogen receptor-α36 is involved in epigallocatechin-3-gallate induced growth inhibition of ER-negative breast cancer stem/progenitor cells 2015

Thus, our study indicated ER-α36 is involved in EGCG's inhibitory effects on ER-negative breast cancer stem/progenitor cells, which supports future preclinical

and clinical evaluation of EGCG as a therapeutic option for ER-α36 positive breast cancer.

https://www.researchgate.net/publication/335091666_Epigallocatechin-3-Gallate_EGCG_Suppresses_Pancreatic_Cancer_Cell_Growth_Invasion_and_Migration_partly_through_the_Inhibition_of_Akt_Pathway_and_Epithelial-Mesenchymal_Transition_Enhanced_Efficacy_whe

Epigallocatechin-3-Gallate (EGCG) Suppresses Pancreatic Cancer Cell Growth, Invasion, and Migration partly through the Inhibition of Akt Pathway and Epithelial–Mesenchymal Transition: Enhanced Efficacy When Combined with Gemcitabine 2019

Epigallocatechin-3-gallate (EGCG), a major polyphenolic constituent of green tea, has been shown to reduce pancreatic cancer growth, but its effect on metastasis remains elusive.

In summary, EGCG may prove beneficial to improve gemcitabine sensitivity in inhibiting pancreatic cancer cell migration and invasion, to some extent through the inhibition of Akt pathway and epithelial–mesenchymal transition.

https://www.researchgate.net/publication/311782892_EGCG_inhibited_bladder_cancer_SW780_cell_proliferation_and_migration_both_in_vitro_and_in_vivo_via_down_regulation_of_NF-kB_and_MMP-9

EGCG inhibited bladder cancer SW780 cell proliferation and migration both in vitro and in vivo via down regulation of NF-κB and MMP-9 2016

EGCG down-regulated the expression of NF-κB and MMP-9 in both protein and mRNA level in tumor and SW780 cells

https://www.researchgate.net/publication/49701530_Green_tea_polyphenol_EGCG_blunts_androgen_receptor_function_in_prostate_cancer

Green tea polyphenol EGCG blunts androgen receptor function in prostate cancer 2010

Androgen deprivation therapy is the major treatment for advanced prostate cancer (PCa). However, it is a temporary remission, and the patients almost inevitably develop hormone refractory prostate cancer (HRPC). HRPC is almost incurable, although most HRPC cells still express androgen receptor (AR) and depend on the AR for growth, making AR a prime drug target.

In a xenograft model, EGCG was found to inhibit AR nuclear translocation and protein expression. We also observed a significant down-regulation of androgen-regulated miRNA-21 and up-regulation of a tumor suppressor, miRNA-330, in tumors of mice treated with EGCG. Taken together, we provide evidence that EGCG functionally antagonizes androgen action at multiple levels, resulting in inhibition of PCa growth.

https://www.researchgate.net/publication/338741198_Preclinical_Pharmacological_Activities_of_Epigallocatechin-3-gallate_in_Signaling_Pathways_An_Update_on_Cancer

Preclinical Pharmacological Activities of Epigallocatechin-3-gallate in Signaling Pathways: An Update on Cancer 2020

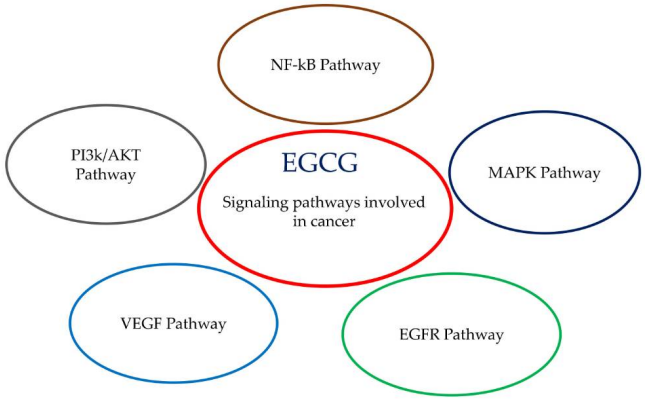

Figure 2. Epigallocatechin gallate (EGCG) involved in the signaling pathways in cancer.