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Therapeutic Potential of Epigallocatechin-3-Gallate in Cancer: A Systematic Review in Human Cancer

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Abstract

The objective of this study is to prove the effectiveness of Epigallocatechin-3-gallate (EGCG) prevent various kinds of cancer types. The method used in this study is a literature review. The source materials for the study were collected from several medical journal databases, such as PubMed Central, Wiley Online Library, Clinical Key, Cochrane, and SpringerLink, to find clinical trial studies that evaluated The ability of epigallocatechin-3-gallate (EGCG) in treating different types of cancer. A total of 293 original publications were examined, and seven studies were found. On the extraction from this research, the data were descriptively summarized. The findings from the seven articles analyzed showed that epigallocatechin-3-gallate (EGCG) has been proven effective in lowering PSA levels in prostate cancer and can effectively relieve acute radiation esophagitis, reduce API and ADI scores suffering from advanced pulmonary cancer with no discernible adverse effects.

Keyword: Cancer, EGCG, Prostat cancer, Lung cancer

INTRODUCTION

Lung, liver, and colorectal cancers are the most widespread carcinomas in men, and The most prevalent malignancies are those of the breast, lung, and colon in women. Certain types of cancer may be more common in certain geographic areas due to differences in socio-demographic factors, such as population age, income and cancer-related risk factors (Brown et al. 2023).

In Indonesia, the 10 most common types of cancer are breast cancer (36.1%), cervical cancer (17.3%), nasopharyngeal cancer (8.2%), lung cancer (7.4%), rectal cancer (6.9%), leukemia (6.7%), ovarian cancer (6.3%), lymphoma cancer (5.3%), colon cancer (4.0%), and prostate cancer (2.0%) (Liu et al. 2021). The etiology of this tumor is not clear, but it is suspected that there is genetic susceptibility and other causative factors (Bray et al. 2024).

Chemotherapeutic agents provide effective therapy in cancer patients, but they may result in negative symptoms like myelosuppression, neuropathy, mucositis, nausea, vomiting, and alopecia. In addition, these drugs are associated with Multidrug Resistance (MDR) which is responsible for more than 90% of cancer patient deaths during chemotherapy (Liu et al. 2021). Thus, ongoing investments are directed at the development of superior replacements

that avoid drug resistance while striking a balance between toxicity and effectiveness. Because plants contain a multitude of bioactive chemicals, herbal remedies has carefully studied as possible sources of anticancer medications.Many plant compounds have shown promising anticancer properties based on various mechanisms, such as inducing apoptosis in cancer cells, inhibiting angiogenesis, and interfering with important signaling pathways involved in cancer progression and metastasis (Abdulridha et al. 2020; Banerjee et al. 2023; Dehelean et al. 2021).

EGCG is the most abundant and bioactive catechin in green tea (Chen et al. 2020). It has been shown that epigallocatechin-3-gallate, or EGCG, possesses antioxidant and anti-inflammatory properties. Through the prevention of carcinogenesis processes including initiation, promotion, and progression, EGCG has shown chemopreventive benefits. Furthermore, this catechin has shown its effectiveness in treating cancer by modifying a number of cell signaling pathways, including the ones that control angiogenesis, apoptosis, proliferation, and the death of different kinds of cancer cells. Additive or synergistic effects of epigallocatechin with chemopreventive agents have been shown to reduce toxicity and enhance anticancer effects (Almatroodi et al. 2020).

This systematic review will discuss how well Epigallocatechin-3-gallate (EGCG) works various types of cancer in humans.

METHODS

Materials and Study Design

A thorough investigation was undertaken from October to November 2024, in which we searched *PubMed Central*, *Wiley Online Library, Clinical Key, Cochrane,* dan *SpringerLink*, using keywords related to "EGCG" or "*Epigallocatechin-3-gallate*" and "*carcinoma" or "cancer*" *and "Response" or "Therapy Response" or "Treatment Response"*. The following terms were employed in the search of all databases. This study reviewed evidence from human clinical trials between 2014 and 2024 to assess EGCG's efficacy in cancer treatment patients not in cell lines or experimental animals. Gender, age, race, and disease duration were not considered.

Methods

The recommended report items for meta-analyses and systematic reviews, or Prism served as the foundation for the writing of this systematic review. This systematic review used the following PICO (population, intervention, control, and outcome) questions: P stands for

population: cancer patients, I (intervention): Epigallocatechin-3-gallate, C: no other disease control, and O (outcome): response to therapy.

Statistical Analysis

Relevant data was taken from the indicated research. Study type, patient characteristics, therapeutic response, and evaluation approaches encompass all important characteristics. Response to treatment was the most significant result evaluated.

RESULTS

The database search yielded 293 initial articles (23 *PubMed Central* articles, 187 *Wiley Online Library* articles, 6 articles from *Clinical Key*, 65 articles from *Cochrane*, and 12 articles from *SpringerLink*. Due to Due to duplicate titles (12 papers) and incomplete research (5 articles in Cochrane), 269 articles were eliminated, while 17 articles were eliminated for having irrelevant titles. Seven publications satisfied the eligibility requirements set forth in this systematic review, after the abstracts and names of the papers were examined (Figure 1).

The seven selected studies were conducted in USA (9,10,12), UK (11); China (Zhao,Zhao) and India (Zhu). There were 1306 cancer patients (350 prostate cancer patients in four studies and 203 lung cancer patient in three studies).

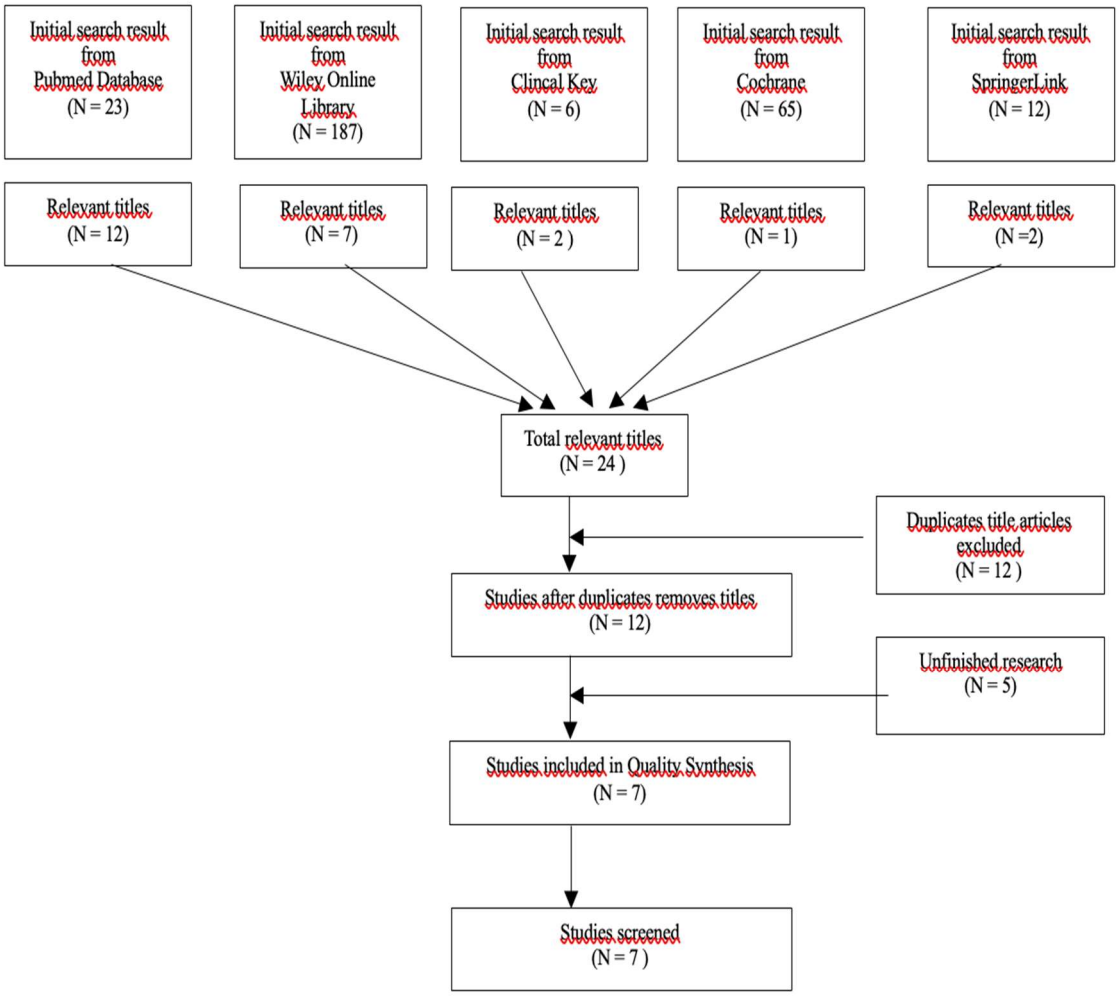

Figure 1. *The article's selection flow diagram*

Four prostate cancer studies with primary or secondary outcomes of PSA levels and other outcomes were included in this systemic review.

A randomized, placebo-controlled trial by Kumar et al. evaluated 400 mg (-)-epigallocatechin-3-gallate (EGCG) is the daily dosage of Polyphenon E® (PolyE) in 97 males between the ages of 30 and 80 who have been diagnosed with either Significant prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) confirmed by biopsy less than 3 months before randomization. Patients included in the study were those without a history of cancer, liver or kidney disease, those not taking steroids or other supplements, or consuming more than 6–12 cups of green tea per day during the study (Kumar et al. 2015).

In this study, plasma catechin and PSA levels were evaluated at the start of the trial, three months later, and at the conclusion. If a person had major adverse effects or PCa, the intervention was stopped. The main objective was to compare the total number of PCa

diagnoses in the two study arms at one year. The PCa rates in the two trial arms were 5/49 (10.2%) Poly E and 9/48 (18.8%) placebo (p = 0.250), with no discernible difference. Serum PSA decreased more in the PolyE arm than in the placebo group, according to an assessment of the overall treatment effect (group PSA difference = - 0.87 ng/ml; 95%CI: -1.66 − 0.09). In addition, the number of subjects experiencing increased plasma catechin EGCG concentrations at 6 ($p < 0.001$) and 12 months ($p = 0.002$) was significantly greater in the PolyE group and the changes in plasma EGCG concentrations at 6 and 12 months were greater in the PolyE group compared to placebo (Kumar et al. 2015).

The cumulative impact of fish oil (FO) while the extract of In 89 men scheduled for a repeat prostate biopsy after an initial negative prostate biopsy, the effects of green tea (epigallocatechin-3-galate, EGCG) supplemental funding on blood PSA, FAS, and Ki-67 levels in prostate tissue were evaluated in a dual-blind randomized controlled experiment by Zhang et al. in 2016. For ninety days before the planned follow-up biopsy, the individuals were split into four groups: FO and EGCG together (1.9 g DHA+EPA/day), EGCG and FO alone (600 mg/day), or a placebo. The research discovered that the placebo group had a substantial rise in FAS (p=0.03) while the EGCG group had a significant drop in Ki-67 (p=0.02) and there was no difference in PSA after intervention between the FO, EGCG and placebo groups. PSA levels were found to be lower in the FO, EGCG groups compared to placebo but were not statistically significant (Zhang et al. 2016).

The subsequent investigation was a 2018 randomized, placebo-controlled phase II trial by Lane et al. in which men with PSA findings between 2.0 and 2,974 ng/mL or between 2,975 and 19.95 ng/mL with negative biopsies results were given lycopene-rich foods or capsules (15 mg lycopene or placebo) or green tea drinks (3 cups) or capsules [600 mg EGCG or placebo] for six months. Metabolite evaluation at six months of intervention was the main outcome, with blood pressure and PSA serving as secondary outcomes. When compared to placebo capsules, the mean lycopene levels were 1.28 [95% CI], 1.09–1.50, P 1⁄4 01.42 (95% CI, 1.21–1.66; $P < 0.001$) times higher in the lycopene-enriched food group and 0.003 times higher in the lycopene capsule group. The median EGCG was 10.7 nmol/L (95% CI, 7.0–32.0) higher in the active capsule group and 20.0 nmol/L (95% CI, 0.0–19.0) higher in the green tea beverage group when compared to placebo capsules (both $P < 0.001$). There was no difference in blood pressure or PSA levels between the groups who drank green tea and lycopene after 6 months of intervention and were also not different from placebo (Lane et al. 2018).

According to Henning et al. (2020), 31 men with prostate cancer participated in a prospective, randomized, open-label, parallel-arm intervention research in which they were

given 800 mg of Quarcetin (GT + Q) or a placebo (GT + PL) or 1 gram of GTE (830 mg GTP) daily for four weeks before to prostatectomy. Those with a history of hepatitis, alcoholism, or other severe physical or mental health conditions, as well as those using luteinizing hormone-releasing hormone agonists or 5-alpha reductase inhibitors, were not allowed to participate in the study, or antiandrogens. Subjects were instructed to abstain from all tea and tea-containing products other than the study tea supplement, and to discontinue nutritional supplements and herbal therapies (eg, quercetin, lycopene, selenium, vitamin E, fish oil, and saw palmetto) (Henning et al. 2020).

Prostate tissue GTP concentration was the study's main aim; blood prostate-specific antigen (PSA) levels and prostate tissue Q concentration were its secondary endpoints. After three weeks of intervention, there was no discernible drop in PSA, no change in plasma PSA across groups, and EGCG and prostate ECG levels in the GT + Q and GT + PL groups were the same. However, Quarcetin concentrations were significantly higher in prostate tissue in men taking GT + Q compared to GT + PL (Henning et al. 2020).

Table 1 Summary of Data Description from The Included Studies

Study	Subject Criteria	Intervention	Outcome
Kumar et al. (2015).	97 male patient aged 30–80 years with a biopsy-based diagnosis of high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP) within three months prior to randomization.	Polyphenon E® (PolyE) including 400 mg daily of (-)-epigallocatechin-3-gallate (EGCG).	PCa rates: 5/49 (10.2%) Poly E compared to a placebo on 9/48 (18.8%) (p = 0.250). Serum PSA: In comparison to the placebo group, the PolyE group's PSA differential was -0.87 ng/ml (95%CI: -1.66 −0.09). Concentrations of plasma catechin EGCG were higher in the PolyE group than in the placebo group at 6 (p < 0.001) and 12 months (p = 0.002).
Zhang et al. (2016).	89 male patient scheduled for a follow-up prostate biopsy after a negative first test.	Samples were divided into four groups (for 90 days before the scheduled follow-up biopsy) : - FO by itself (1.9 g DHA+EPA daily) - EGCG by itself (600 mg daily) - The combination of EGCG and FO - A placebo	Ki-67 occurred in the EGCG group (p=0.02) FAS occurred in the placebo group (p=0.03) No. difference in PSA after intervention between the FO, EGCG and placebo groups.
Lane et al. (2018).	133 male patient having PSA readings between 2.0 and 2.974 ng/mL or a negative biopsy with a reading between 2.975 and 19.95 ng/mL	lycopene-rich meals or supplements (15 mg lycopene or placebo) and green tea beverage (3 cups) or pills (600 mg EGCG or placebo) for six months.	The lycopene and green tea groups did not vary in blood pressure or PSA levels.
Henning et al. (2020).	31 male patient with prostate cancer without 5-alpha reductase inhibitors, antiandrogens, luteinizing hormone-releasing hormone agonists, or a history of hepatitis, alcoholism, or other serious medical or mental disorders	For four weeks before a prostatectomy, take 800 mg of quercetin (GT + Q) or a placebo (GT + PL) together with 1 gram of GTE (830 mg GTP) every day.	Following three weeks of intervention, there was no discernible drop in PSA or variation in plasma PSA across the groups.

Study	Subject Criteria	Intervention	Outcome
Zhao et al. (2015).	37 patients were diagnosed with pathologically unresectable stage IIIA or stage IIIB lung cancer, aged >18 years with ECOG PS 0–1. Patients had not received prior systemic chemotherapy or radiation to the thorax.	EGCG was dissolved in 0.9% saline and stored at 4 °C. For esophageal application, patients were asked to slowly swallow 15 ml of EGCG solution with a concentration of 440 lmol/L three times a day during radiation.	EGCG taken orally is a safe and efficient treatment for acute radiation-induced esophagitis.
Zhao et al. (2019).	83 patients with stage IIIA or medically inoperable lung cancer aged 18 years with a Karnofsky score of 70.	Patients were divided into three groups: - Group A : EGCG (440 lmol/L) given simultaneously with RT, - Group B : EGCG (440 lmol/L) given immediately after extremely mild esophagitis occurred during RT - Group C: mLDG group (lidocaine 0.16 mg/mL, dexamethasone 0.02 mg/mL, and gentamicin 0.16 mg/mL) given immediately after extremely mild esophagitis occurred during RT.	EGCG can effectively alleviate acute radiation esophagitis and the API and ADI scores were much lower in EGCG-treated individuals.
Zhu et al. (2021).	83 lung cancer patients, including 45 non-SLCL lung cancer patients and 38 SCLC patients	Patients were divided into three groups: - Group A : EGCG (440 lmol/L) given simultaneously with RT, - Group B : EGCG (440 lmol/L) given immediately after extremely mild esophagitis occurred during RT - Group C: mLDG group (lidocaine 0.16 mg/mL, dexamethasone 0.02 mg/mL, and gentamicin 0.16 mg/mL) given immediately after extremely mild esophagitis occurred during RT	The EGCG group had a greater objective response rate (ORR) (p = 0.045). 5-year PFS was 9.3% with traditional treatment and 33% with EGCG. 30.3% against 33.3% was the 5-year OS. Compared to patients receiving conventional therapy, those receiving EGCG had reduced mean esophagitis and adjusted pain indices..

There are three studies related to the effectiveness of EGCG on lung cancer included in this systemic review. The outcomes of the three studies vary from the effects of EGCG on pain and the incidence of acute radiation-induced esophagitis reported from two studies and the effects of EGCG on the response rate of therapy, PFS, OS, and the effectiveness of EGCG in treating esophagitis are all factors to consider.

The study by Zhao et al., in 2015 involving 37 patients, aged >18 years, with ECOG PS 0–1, who were diagnosed with stage IIIA or stage IIIB lung cancer that was pathologically incurable. The patient had not previously had thoracic radiation treatment or systemic chemotherapy. All patients underwent 3D-CRT or IMRT, which is 1.8–2.0 Gy per day, five days a week. Patients who were pregnant or nursing, had an EGCG allergy or hypersensitivity, or had mediastinal tumors or metastatic lymph nodes invading the esophagus were not included in the research. EGCG was kept at 4°C after being dissolved in 0.9% saline. During radiation therapy, patients were instructed to gently drink 15 milliliters of a 440 lmol/L EGCG solution

three times a day. The study showed that oral administration of EGCG is an effective and safe method for treating acute esophagitis due to radiation (Zhao et al. 2015).

Further research conducted by the same researcher previously Zhao et al. in 2018 involved 83 patients with stage IIIA or medically inoperable lung cancer aged 18 years with a Karnofsky score of 70. Patients with allergies or hypersensitivity to EGCG; pregnant or breastfeeding; and patients who had previously received radiation to the thorax were left out of the research sample. Patients were divided into three groups: group A patients were given EGCG (440 lmol/L) given simultaneously with RT, group B patients were given EGCG (440 lmol/L) given immediately after very mild esophagitis occurred during RT, and group C patients were given mLDG (lidocaine 0.16 mg/mL, dexamethasone 0.02 mg/mL, and gentamicin 0.16 mg/mL) given immediately after very mild esophagitis occurred during RT. All three interventions were dissolved in 0.9% saline solution given three times a day during radiation and outcomes were monitored for up to 2 weeks after radiation (Zhao et al. 2019).

Evaluating the relative effectiveness of EGCG in reducing Gradual esophagitis with radiation therapy for lung cancer in comparison to the standard regimen was the main goal. The NRS-based Dysphagia Index (ADI), Adjusted Pain Index (API), and maximal esophagitis score were secondary objectives. Although there was no discernible difference in response rates between the three therapy groups, EGCG medication might successfully reduce acute radiation esophagitis in patients with advanced lung cancer without causing any noticeable adverse effects. For the treatment of acute esophagitis, EGCG prevention is thus preferable for therapeutic use. In addition, API and ADI were significantly lower in patients receiving EGCG compared to patients treated conventionally (Zhao et al. 2019).

Further research conducted by Zhu et al., in 2021 consisting of 83 lung cancer patients, 45 of whom had non-SLCL lung cancer and 38 of whom had SCLC. The identical intervention used in the 2018 research by Zhao et al. was split up into three groups. The OS and median PFS, however, were not substantially extended, the EGCG group's Objective Response Rate (ORR) was greater than that of patients receiving conventional treatment ($p = 0.045$). When EGCG was used instead of standard therapy, compared to 9.3%, the 5-year PFS was 33%, and the 5-year OS was 30.3% against 33.3%. The mean esophagitis index and adjusted pain index in patients with EGCG application were lower than in conventional treatment (Zhu et al. 2021).

DISCUSSION

Carcinogenesis is known to be different molecular and cellular changes that take place via a multistep/multipathway process with unique but closely connected initiation, promotion,

and progression stages. Therefore, effective chemopreventive agents must intervene early in the carcinogenesis process to eliminate premalignant cells before they become malignant (Siddiqui et al. 2015).

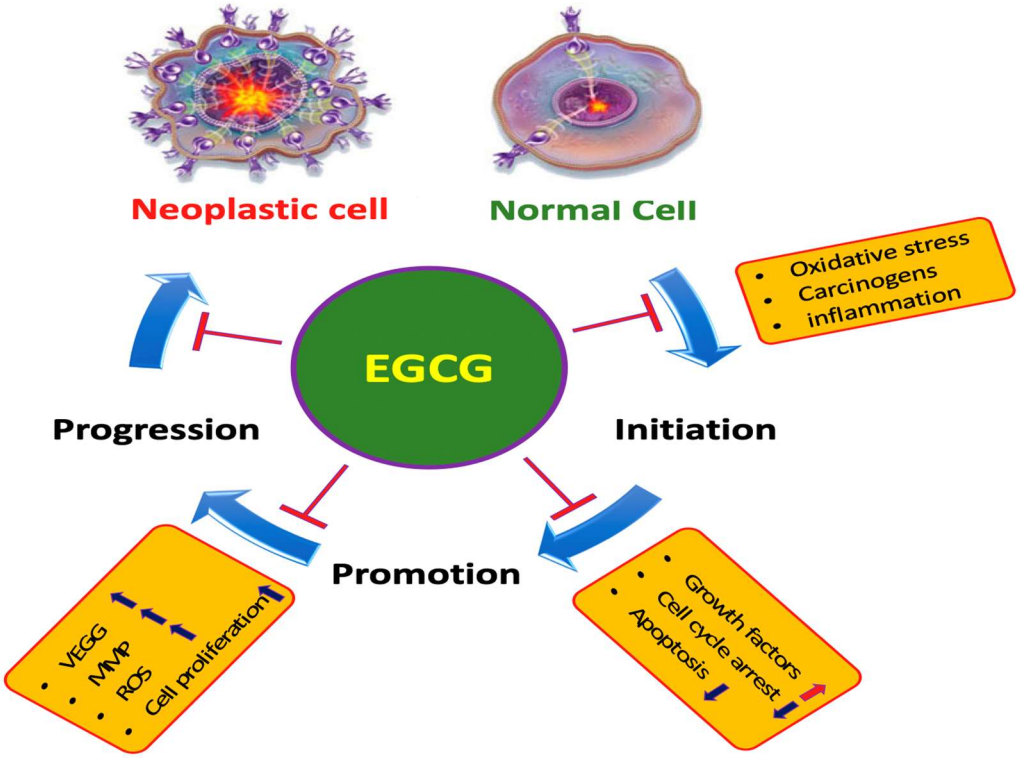

***Figure 2**. The Role of Epigallocatechin-3-Gallate (EGCG) in Inhibiting the Carcinogenesis Process (Almatroodi et al. 2020).*

Elevated blood Prostate-Specific Antigen (PSA) levels are the most frequent first laboratory finding in prostate cancer screening since the majority of men with early-stage prostate cancer do not exhibit symptoms. Because both benign and malignant illnesses may raise blood indicators, PSA is a very sensitive screening method that is also somewhat general and inaccurate. From the four studies, it can be concluded that a greater decrease in PSA levels was found in samples given EGCG, but this decrease was also influenced by time. ECGC administration for 1 year showed a significant difference, while EGCG administration for 6 months and 3 weeks did not provide significant changes and differences compared to placebo even though it was given at a higher dose.

EGCG decreases PSA levels, thereby suppressing PSA growth inside LNCaP cells. PC-3 cell growth is inhibited by EGCG via the stimulation of the signaling pathways for extracellular signal-regulated kinase (ERK1/2) and mitogen-activated protein kinase (MEK). EGCG inhibits 22Rv1 cell invasion and migration via regulating the synthesis of proteins in

VEGF, uPA, angiopoietin 1 and 2, MMP-2, and MMP-9. In PC-3 cells, the pro-apoptotic splicer isoform caspase 9 was expressed more when EGCG and cisplatin were combined. EGCG suppressed vasculogenic mimicry through inhibition of the Twist/VE-Cadherin/AKT pathway in PC-3 cells (Hao et al. 2022).

It was shown that EGCG has anticancer properties, inhibiting the growth of cancer cells and triggering the extracellular signal-regulated kinase pathway in a way that is dependent on time and concentration. The strongest catechin at stopping cell development is EGCG. The inhibition induced by EGCG has been shown to be enhanced through apoptotic cell death, as observed by changes in nuclear morphology and DNA fragmentation (Almatroodi et al. 2020).

EGCG has a significant impact in affecting a number of molecular pathways, including apoptosis, the AKT pathway, and cell cycle control, even if the precise molecular mechanisms by which it affects prostate cancer remain unknown. Clinical experiments have shown that EGCG may limit the multiplication of cancer cells, thus the potential advantages of combining it with other natural chemicals and medicinal drugs should not be ignored. Furthermore, increasing the bioavailability of EGCG through its integration with other dietary components has shown promising results (Kumar et al. 2024).

EGCG has potent antiproliferative and antitumor properties. EGCG stimulates the production of oncogenes like the proto-oncogene c-Myc and tumor suppressor genes like p53 and p21. Additionally, EGCG supports the stability of the tumor suppressor gene p53, which prevents lung cancer cells from growing anchorage-independently. MDM2-mediated p53 ubiquitinylation is inhibited when EGCG interferes with the connection between p53 and the oncogene Murine Double Minute 2 (MDM2). EGCG can increase β-catenin and p53 levels and decrease the expression of vimentin, VEGF, p-AKT, HIF1α, COX-2, and p-ERK proteins (Figure 3) (Zhang et al. 2019; Zhao et al. 2021).

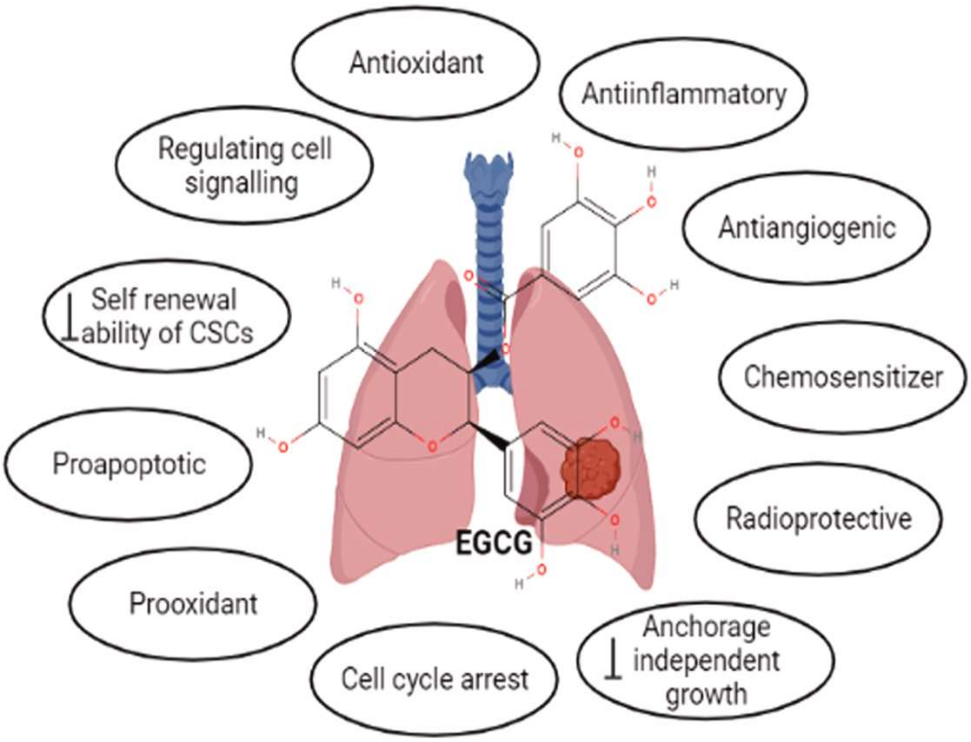

Figure 3. *Chemopreventive and Therapeutic Activity of EGCG in Lung Cancer (Sehgal et al. 2023).*

EGCG prevents lung cancer by inhibiting CD133+ cells' CLOCK protein, which preserves cancer stem cells' capacity for self-renewal and prevents A549 and H1299 cells from forming spheres. Inhibition of the Wnt/β-catenin System disrupts the properties of cancer stem cells. EGCG intervention can downregulate Nuclear Enriched Plenty Transcript 1 (NEAT1), a lncRNA that has been found abundantly in NSCLC stem cells, leading to the loss of stem cell properties and upregulation of Copper Transporter (CTR1) (Figure 4) (Sehgal et al. 2023).

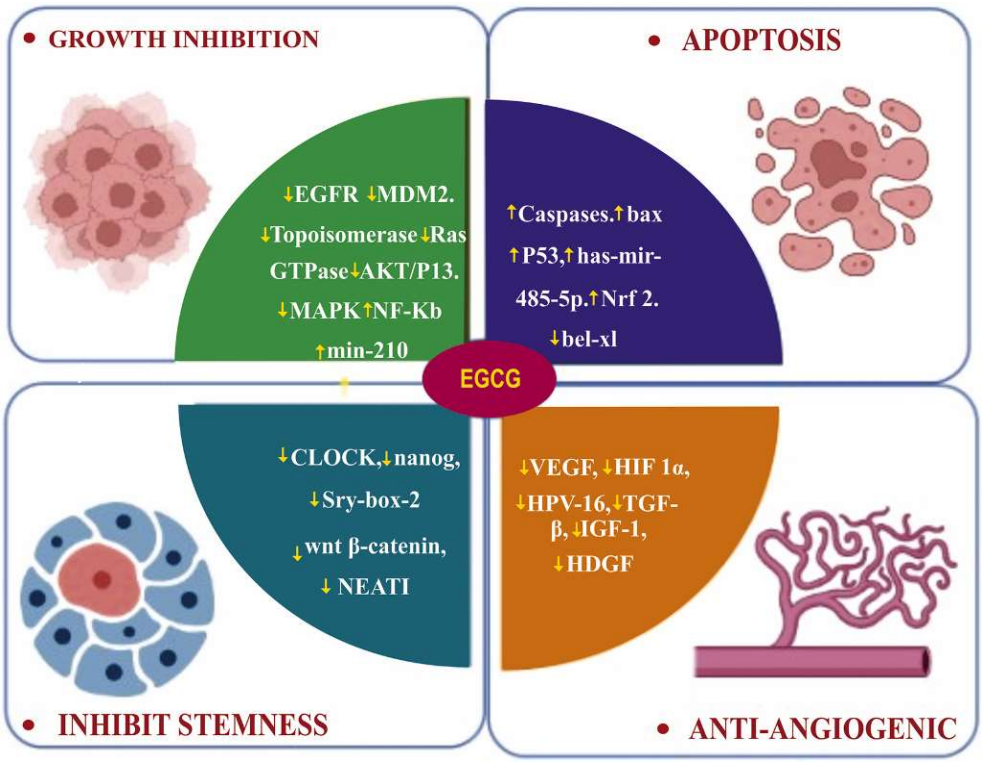

***Figure 4**. Effect of EGCG on Modulating the Expression of Molecules Involved in Lung Carcinogenesis (Sehgal et al. 2023).*

CONCLUSIONS

It has been shown that epigallocatechin-3-gallate (EGCG) possesses antioxidant and anti-inflammatory properties. It has been shown that EGCG effectively reduces PSA levels by blocking carcinogenesis processes such as initiation, promotion, and progression; however, the rate of reduction varies with time. Additionally, EGCG may reduce API and ADI scores in advanced lung cancer and successfully treat acute radiation oesophagitis without causing any noticeable adverse effects.

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