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EXPLORING INTEGRATIVE APPROACHES: EGCG'S POTENTIAL IN COMBATING PROSTATE CANCER

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ABSTRACT – Prostate cancer is the most common cancer in males and one of many types of malignancies that are said to be prevented by drinking green tea and Epigallocatechin-3-gallate (EGCG) intervention. However, epidemiological studies have produced conflicting results regarding the anti-cancer effects of EGCG. In recent years, numerous researchers have demonstrated the effectiveness and safety of green tea polyphenols, including EGCG alone and in combination therapies, through *in vivo* and *in vitro* studies. Nevertheless, the molecular mechanisms underlying the anticancer potential of EGCG remain poorly understood. To evaluate the prevention and treatment of prostate cancer, it is critical to have a better understanding of the precise mode of action of EGCG against the growth and progression of prostate cancer. With a focus on the molecular mechanisms of action of EGCG, such as influencing tumour growth, apoptosis, androgen receptor signaling, cell cycle, and various malignant behaviors, we present information regarding the anti-cancer effects of EGCG in the prevention and treatment of prostate cancer in this review.

KEYWORDS: EGCG, Prostate Cancer, Signaling Pathways, Clinical trials.

INTRODUCTION

With 12,76,106 new cases and 3,58,989 deaths (3.8% of all deaths from cancer in men), Prostate cancer (PCa) is the second most common malignancy in men worldwide (after lung cancer)[1]. According to Rawla et al[2], PCa incidence and mortality are both correlated with ageing globally, with an average age of 66 at diagnosis. Due to population growth and ageing, it is predicted that there will be almost 2.3 million cases of PCa globally and 7,40,000 deaths by 2040[3]. The well-known risk factors for PCa are age, race, and a family history of the disease[4]. There are numerous reports that claim low plasma-selenium and -tocopherol concentrations and high calcium intake in the diet increase the risk of PCa[5]. Androgens are necessary for the growth and development of the prostate gland, and it has long been believed that high levels of them are a major factor in the development of PCa[6,7]. According to recent studies, the majority of prostate tumours respond to androgen deprivation therapy until the point at which they develop an androgen-independent growth mechanism[8,9].

Multiple strategies have been proposed so far to contain the growth and progression of PCa. One such strategy is the use of naturally occurring compounds of plant origin. Ayurveda, Homoeopathy, and Unani are just a few of the indigenous medical systems that heavily rely on medicinal plants, including tea plants, which are grown in places like China and India[10]. Researchers and health professionals have begun to pay close attention to tea (*Camellia sinensis*), which is the second most consumed beverage after water worldwide[11-14]. There are many different types of tea, but green and white tea are thought to be the healthiest because they contain the highest concentrations of tea catechins, which make up 30–40% of their dry weight along with only trace amounts of flavonoids. EGCG is well known to have anti-cancer, anti-inflammatory, and anti-aging properties. Epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and catechin are the four main catechins present in tea[15,16]. According to Stewart et al[17], catechin and EGCG are the primary antioxidants in green tea, accounting for about 30% of its overall antioxidant capacity. Numerous health conditions, including cancer, have been studied in-depth using EGCG as a preventive and therapeutic agent[18-24]. The ability of EGCG to inhibit the growth of multiple malignant cells and to induce apoptosis has also been emphasized in many studies[24-29]. EGCG controls cancer via blocking of various signaling molecules/pathways like cell cycle regulation, JAK/STAT, MAPK, PI3K/AKT, Wnt and Notch[30], apoptotic pathway, and angiogenesis[31], which in turn influence the molecular events that ultimately result in carcinogenesis. In this review, we will assess the findings derived from *in vitro, in vivo,* and clinical trials that have been carried out to examine the protective effects of EGCG against PCa. Furthermore, we will formulate research queries that could serve as a foundation for forthcoming investigations in this realm.

PROSTATE CANCER

Prostate intraepithelial neoplasia is the first stage of the malignant transformation of prostate cells, which then progresses to localized PCa, local invasive adenocarcinoma, distant metastasis, primarily to the lymph nodes or bone, and finally an androgen-independent phenotype[32]. The most well-known premalignant lesion and precursor to prostatic carcinoma is prostatic intraepithelial neoplasia. The progression of PCa results in progressive abnormalities of phenotype and genotype, indicating impairment in cell differentiation and regulatory control. The androgen receptor (AR) is a crucial transcription factor that triggers the tumorigenesis and progression of androgen dependent PCa[33,34] (Figure 1). Hence, the

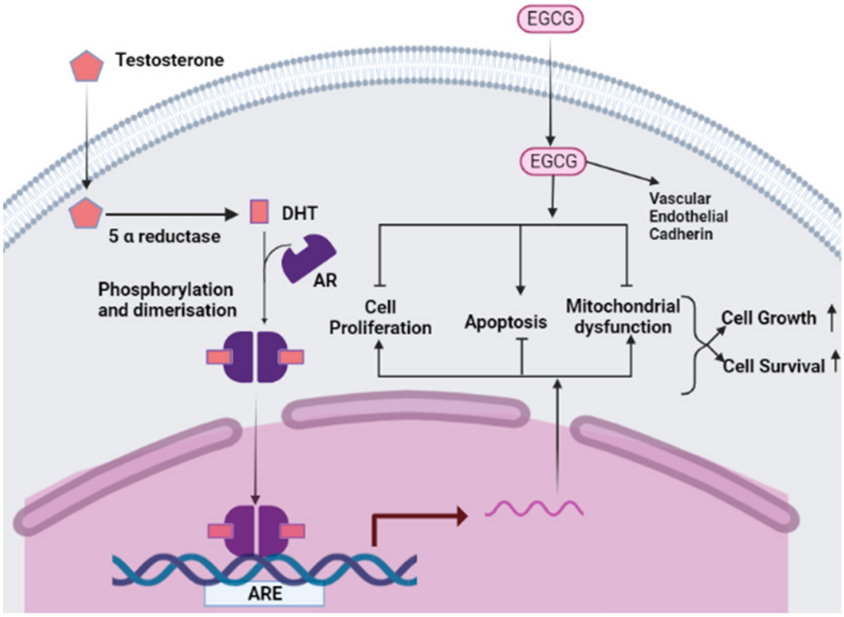

Figure 1. Normal Prostrate cancer growth and development and intervention by EGCG: testosterone after entering the prostate cell is converted into Dihydrotestosterone (DHT) by 5α-reductase. DHT binds to androgen receptor (AR) and induces its phosphorylation and dimerization. These AR dimers enter the nucleus and attaches to androgen response elements (ARE) along with other coactivators, thereby leading to the activation of target genes. This signals the upregulation of cell proliferation, mitochondrial dysfunction and downregulation of Apoptosis and thus resulting in enhanced cell growth and cell survival. On the other hand, EGCG may prevent prostate cancer by modulating the above events. (Modified from Feldman and Feldman[48]).

initial phase of treatment for androgen-dependent PCa involves androgen depletion therapy. However, these cancerous cells eventually get transformed into the currently incurable androgen-independent PCa (AIPC)[35,36]. Androgen deprivation therapy has been found to be futile at this point since the cancerous cells are now hormone-insensitive and capable of growing without androgen, leading to metastasis[30,37,38]. A number of investigations have demonstrated that aberrant AR expression and persistent AR signaling are important contributors to the development of AIPC[39,40]. Even in the presence of low testosterone levels and/or an absence of androgens, the enhancement of AR-mediated signals in AIPC cells leads to increased cell proliferation[1,41,42] (Figure 2). Prostate intracrine androgen biosynthesis, AR

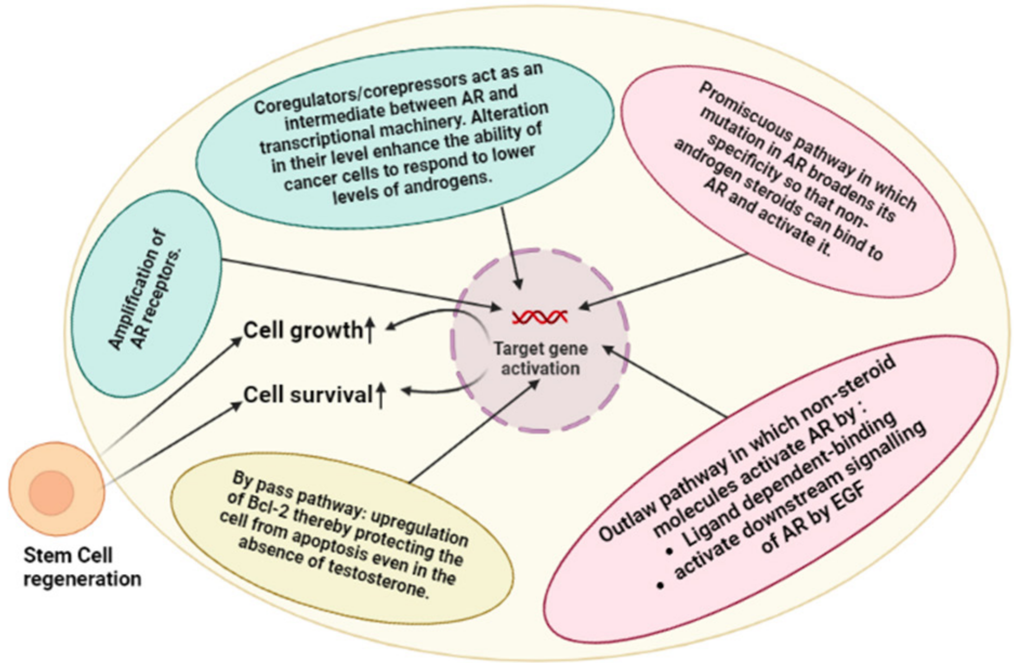

Figure 2. Schematic representation of possible pathways for development of androgen independent PCa (AIPC): (i) amplification of AR receptors mostly by enhanced gene expression and increased coactivators are dependent on both androgen and androgen receptors, (ii) promiscous and outlaw pathways are independent of androgens but depend upon AR, (iii) by pass pathway and prostate cancer stem cell which continuously supply new cancer cell population are independent of both androgen and AR[49].

amplification, mutation, AR-splice variants, modification of AR co-regulators, modulation of oncogenes and tumour suppressor genes, and differentiation of neuroendocrine cells are the mechanisms that contribute to the progression of AIPC[38]. The first five pathways depend on ongoing AR signaling activation and are, therefore, AR-dependent. The last two pathways are not dependent on AR signalling[43,44] (Figure 2). Both *in vitro* and *in vivo* studies of AIPC have linked AR amplification and overexpression to the disease[43,45]. Even in the presence of low levels of circulating androgen, aberrant gene amplification may result in the overexpression of AR and subsequently enhance AR-androgen ligand binding[39]. Additionally, AR mutations may also be present in PCa cells. These mutations change the AR ligand-binding domain, increasing the binding specificity to other endogenous steroid ligands (such as progesterone, corticosteroids, and oestrogen)[46], thereby increasing AR transactivation activity. The lack of a ligand-binding domain in tumor cells allows them to become constitutively active, bypassing the need for androgens[18]. The overall AR activation in AIPC may also be influenced by the coactivator/corepressor ratio. In AIPC cells, co-activators are overexpressed, and they regulate AR activity to help the cells become androgen-independent[47]. Contrarily, it has been observed that the co-repressor proteins are down-regulated in AIPC, leading to an increase in AR-mediated transcriptional activity[43].

The development of treatment resistance and subsequent progression to AIPC were caused by the progression of PCa to neuroendocrine differentiation of PCa cells (NEPC)[48-50]. This pathway is classified as an AR-independent pathway, in contrast to the previously discussed pathways. NEPC cells continuously secrete neuropeptides like serotonin and bombesin, which have paracrine effects on neighboring cells despite the absence of androgen. These neuropeptides increase the ability of PCa cells to proliferate, move, and spread[51]. Through the manipulation of the Bcl-2 oncogene and PTEN (phosphatase and tensin homologue deleted on chromosome-10) tumour suppressor genes, AIPC cells also acquire the capacity to endure androgen castration. PTEN controls the PI3 pathway's activity negatively, which is linked to cell migration, survival, and proliferation. The downregulation of PTEN results in constitutive PI3 pathway activation, which in turn promotes the translocation of AR molecules and AR-mediated transcriptional activity[52].

EGCG AND PCA

Structure and Mode of Action of EGCG

EGCG is a key active tea ingredient with a variety of health advantages[42,43]. It is the ester of epigallocatechin and gallic acid and has a polyhydroxy structure that makes it highly hydrophilic and low in lipophilia. One bag of green tea is thought to contain 80–100 mg of polyphenols, of which 25–30 mg come from EGCG. According to Botten et al[53], the structural components of EGCG include a benzenediol ring (A) attached to a tetrahydropyran moiety (B), a pyrogallol ring (C), and a galloyl group (D). The hydroxyl groups on the rings are thought to be responsible for their biological activity because they interact with other biological components through hydrogen bonds and electron transfer. These are the primary factors influencing the antioxidant activity of EGCG[45]. EGCG is water-soluble and is not impacted by high temperatures; exposure to conditions like boiling water cannot significantly affect the stability of the molecule[54]. The powerful antioxidant and chelating properties of EGCG make it useful for preventing a number of diseases linked to an increase in oxidative stress[13]. EGCG is considered the most effective modulator of prostate carcinogenesis[55-59]. EGCG has the potential to inhibit a variety of proteins linked to cancer, including the cyclin-dependent kinase inhibitor p27, Bcl-2, Bax, matrix metalloproteinases (MMP2 and MMP-9), androgen receptor, EGF receptor, and activator proteins-1[60]. Similarly, EGCG can inhibit PCa development by inducing apoptosis and inhibiting proteasome activity, B-alfa and p27 proteins as well[61-64] (Figure 3).

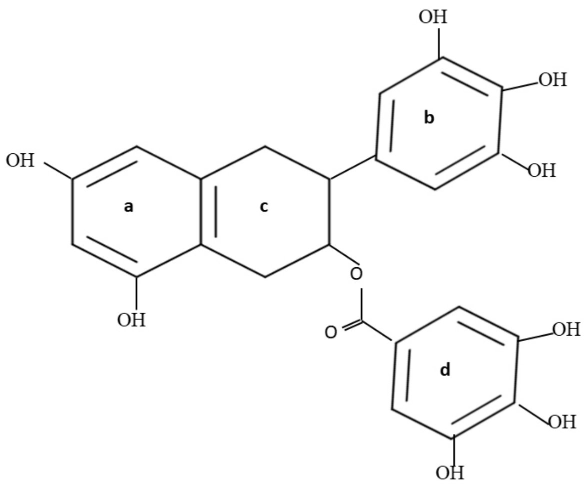

Figure 3. Structural composition of (−)-epigallocatechin gallate (EGCG).

Absorption, metabolism, and bioavailability of EGCG

Oral EGCG has been reported to be absorbed into the blood through the gastrointestinal tract to play its biological role[65]. It takes around 90 minutes for EGCG to reach its peak plasma level after oral consumption[66]. According to Hara et al[67], ECGC also interacts with saliva upon entering the mouth and some concentrations of EGCG in saliva have also been found after drinking tea. In the intestine, the metabolic interaction of EGCG with gut microbiota, its oxidation and efflux decrease the bioavailability of EGCG subsequently affecting its biological activity[68]. According to Nakagawa and Miyazawa[69] the maximum concentration of EGCG was 0.012% and 0.32% of ingested EGCG in fasted rat and human plasma, respectively, thereby demonstrating the poor bioavailability of EGCG. Studies have reported that the intestinal stability of EGCG is affected by change in temperature and intestinal pH. EGCG is prone to decomposition in intestinal pH conditions. According to Zagury et al[70], under simulated conditions of intestinal pH, the recovery rate of free EGCG was found to be less than 10%. Further, EGCG is subjected to action of gut microbiota. In a study, EGCG was reported to be hydrolyzed by gut microbiota (such as *Enterobacter aerogenes*, *Raoultella planticola*, *Klebsiella pneumoniae* etc.) into EGC and gallic acid, and EGC was further degraded by cascade of conversions, thereby resulting in 5-(3,5-dihydroxyphenyl)-4-hydroxyvaleric acid as the main metabolite of EGCG which was found in rat cecal contents and feces[71].

According to Schantz et al[72] microbial esterase activity is presumably responsible for the cleavage of gallate moieties of EGCG during its passage through the small intestine. EGCG is also converted into metabolites via methylation, sulfation, and glucuronic acid through metabolic enzyme II of hepatic and intestinal cells[73]. Among these pathways, methylation is thought to be a significant metabolic pathway, producing important metabolites such as 4′-O-methyl-EGCG, 4′,4′-dimethyl-EGCG-3′-glucuronate, 3′,4′- or 3′,5′-dimethyl-EGCG-4′-O-glucuronic acid[74]. Thus, the chemical instability decreases the absorption and bioavailability of EGCG. Furthermore, the poor permeability of intestinal EGCG also affects its bio-availability. Since specific receptors for the transport of EGCG are not found on the surface of intestinal epithelial cells, EGCG is mainly absorbed through passive diffusion including acellular and transcellular diffusion. Further, most of the absorbed EGCG is pumped back into the intestinal lumen through active transportation via efflux proteins[65]. The part of EGCG that enters the blood through intestinal absorption is circulated to other parts of the body. Some metabolic pathways of EGCG such as methylation, glucuronidation and sulfation, have also been reported to occur in blood. Among these, methylation considered the major metabolic pathway, results in formation of 4′-O-methyl-EGCG, 4′,4′-dimethyl-EGCG-3′-glucuronate, 3′,4′- or 3′,5′-dimethyl-EGCG-4′-O-glucuronic acid[74]. The liver also causes acidification of EGCG and converts it into EGCG-4′′-O-glucuronic acid complex. Additionally, the amount of EGCG that the liver removes from the blood is secreted into the bile. From the small intestine, a large amount of EGCG may remain unabsorbed or after enterohepatic recycling, is passed into the large intestine which is further extensively degraded by bacteria present in the colon. Catechins (EGCG, ECG, EC, EGC) incubated with human fecal suspension were metabolized to 3′,4′,5′-trihydroxyphenyl-γ-valerolactone, 3′,4′- dihydroxyphenyl-γ-valerolactone, 3′-hydroxyphenyl-γ-valerolactone and other metabolites[75]. These metabolites further undergo side-chain shortening to produce C-6−C-1 phenolic and aromatic acids that enter the bloodstream and are excreted in urine[76].

Cancer preventive effects of EGCG

Numerous epidemiological studies have linked dietary habits to PCa risk. Because of their ancient traditional diets, Asian men have a low incidence of PCa[77,78]. Low fat, high fiber diets are common among Chinese and Japanese people, which may contribute to chemoprevention and the low incidence of cancer in these populations, including PCa[11,41,79-82]. According to another similar study[83], men who drank green tea five or more times per day had a 29% high negative correlation with PCa. Green tea catechins (GTC), including EGCG, may be able to inhibit cell division, cell cycle progression, and induce apoptosis through a variety of molecular mechanisms[57,84,85]. The chemopreventive and anticancer effects of EGCG against PCa have not yet produced conclusive results, despite epidemiological evidence to the contrary[86].

Cell line studies

It is challenging to ascertain how EGCG can lower the incidence of PCa due to the conflicting and unclear epidemiological evidences. Therefore, numerous studies have been conducted to determine the precise molecular mechanism by which EGCG inhibits the development and growth of PCa. In a series of studies conducted on different PCa cell lines, researchers have extensively investigated the effects of EGCG (Epigallocatechin gallate), a polyphenol found in green tea. The results from these studies collectively demonstrate the potential of EGCG as a promising therapeutic agent for PCa treatment. The findings of some studies suggest that EGCG has the potential to modulate cell cycle regulators, cell proliferation[87,88], vascular endothelial cadherin[89], and mitochondrial signal transduction pathways in PCa. Among these, the apoptotic pathway is found to be the main target of EGCG in PCa. Table 1 provides information

Table 1. Studies demonstrating how EGCG affects various molecules within prostate cancer cell models.

Cell line/model	Dose	Findings	Reference
DUPRO and LNCaP cells	10μg/ml GTP, 20 μM| EGCG	Reduced class I histone deacetylase (HDAC) activity /expression and EZH2 and H3K27me 3 levels in prostate cancer cells.	90
LNCaP prostate cancer	2-4 mg/L (about 5-10μm) Cur, 1μM Arc and 40μM EGCG	In LNCaP cells both Arc and EGCG increased pro-apoptotic effect of Cur.	91
DU145 cell line	EGCG (1.5-7.5μM)	Reduced ionizing radiation induced apoptosis (P< .001), Radiotherapy and EGCG together 1.5 -fold increase in Manganese superoxide dismutase levels.	92
(PC)3 Cells	30 and 100μg/ml PE (polyphenol)	Decreased cell viability and proliferation. Mitochondrial dysfunction and downregulation of Akt activation.	93
LNCaP cells	5-10μM curcumin 40μM EGCG	Improve synergistically in vitro antiproliferative by 40% in androgen sensitive LNCaP cells. It also enhanced cell apoptosis induction and cell cycle perturbation.	94
PC-3 Cells	EGCG (10,20,40,80 μm) for 24 hour and performed 3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide	80μM EGCG decreased cell viability. EGCG downregulated the expression of vascular endothelial cadherin	89
LNCaP cells and PC-3 Cells	10-80μg/ml of GTP for 24 hours	Dose dependent inhibition of class I HDAC enzyme activity and its protein expression.	81
DU145 cells and RWPE-1 cells	10-50 μg/mL LEGCG on DU145 cells and 40-50μg/mL on RWPE-1 cells	A little higher inhibition rate on DU145 cells but exhibited high cytotoxicity on RWPE-1 cells	46
DU-145 cells	EGCG (40μg/ml)	Reduced cell number by 20% with 24 h and 4h treatment	96
PC-3 cells	80μmol/L Zn2+ and 80μmol/ L EGCG	Could induce apoptosis of PC-3 cells and cause sufficient damage to cells to rest in Necrosis.	97
Human beings	Two 300mg green tea leaf derived extract Capsules (600mg/d EGCG)	Men at increased risk of prostate cancer sticked to lycopene and green tea diet and capsule intervention for 6 months with some side effects	98
DU145 cells	100-200μM EGCG	Inhibition of TGF-α caused activation of erbB1 followed by inhibition of Shc activation without alteration in protein level.	33
CWR22Rv1	0, 0.1, 1, 5, 10, or 50μM EGCG, genistein or quercetin	Inhibition ability of CWR22Rv1 cells to form colonies at doses >5μM whereas 5μM genistein produced affects not significantly different from vehicle treated control cells.	86
PC-3 AP-1 Human PCa cells	EGCG (20 or 100 μmol/L) and SFN (25 μmol/L)	AP-1 activation attenuated and 100mg/kg SFN downregulated Nrf-2 dependent genes.	99
LNCaP cells	20μM EGCG and DHT	It showed a similar viability as control cells without DHT treatment. It also inhibited growth to level similar to cells with no stimulation of androgen.	100
PC3 cells	1 and 25μM EGCG	1μM EGCG sufficiently increased the proportion of apoptotic bodies and reduce cell survival.	101
DU-145 cells	5-40 μg/ml EGCG	Inhibited FCM- induced production of pro-MMP-2, and pro and active forms of MMP-9. Even 5μg/ml EGCG was able to inhibit synthesis of MMP-2 and -9	102
LNCaP cells and PC3 and DU145 CaP cell lines	EGCG on growth and (0-200μM) and on cell death (0-50μM)	In dose dependent manner EGCG decreased proliferation of all CaP cancer cells with increase in apoptosis from 30 to50μM.	103

on the dose of EGCG and particular cell lines that were used in various studies. EGCG has been shown to inhibit the growth of PCa cells through various mechanisms. For instance, when DU145 cells were treated with Lipophilized EGCG, a derivative of EGCG, it resulted in a significant inhibition of cancer cell growth[46]. Another similar study showed the augmentation in growth inhibitory effects of EGCG on a variety of cancer cells when used in conjunction with ibuprofen[90-96].

In addition to inhibiting cancer cell growth, EGCG is also a promising candidate to induce apoptosis (programmed cell death) in PCa cells. A concurrent increase in apoptosis and decreased proliferation in all PCa cells upon treatment of LNCaP cells with EGCG has been revealed[97-103]. Moreover, a combination of EGCG with Arctigenin (Arc) and curcumin enhanced the anti-proliferative effect and increased apoptosis in LNCaP cells, suggesting a potential combinatorial approach for PCa treatment[91]. Similarly, a synergistic effect between EGCG and curcumin in inducing apoptosis and perturbing the cell cycle in androgen-sensitive LNCaP cells was also reported[94].

The benefits of EGCG are not restricted to a few cell lines; it also showed promising effects in several PCa cell types. In PC3 cells, EGCG and zinc were found to induce apoptosis, leading to cell damage and arrest in necrosis[97]. Additionally, EGCG treatment led to decreased cell viability and downregulated expression of Vascular Endothelial Cadherin, further indicating its potential for inhibiting cancer cell growth and impairing cell function[89]. In addition, three substances —EGCG, genistein, and quercetin — synergistically reduced the proliferation of CWR22Rv1 CaP cells, suggesting a potential combination therapy for PCa[87].

EGCG's actions on PCa cells extend beyond direct growth inhibition and apoptosis induction. In DU145 cells, EGCG, together with silymarin and genistein, was shown to inhibit mitogenic signaling pathways and cell cycle regulators, leading to the inhibition of TGFα-induced activation of erbB1 and Shc[33]. Treatment of DU145 cells with EGCG also inhibited the production and activation of certain matrix metalloproteinases (MMPs), further supporting its potential as an anti-cancer agent[102]. Furthermore, EGCG has been implicated in epigenetic regulation, offering new insights into its anti-proliferative mechanisms. Treatment of LNCaP cells with GTP (green tea polyphenol) resulted in the inhibition of class 1 HDAC enzyme activity and potentially affecting gene expression and cancer cell growth[81]. Moreover, GTP and EGCG treatment induced the expression of TIMP-3 mRNA and protein, reduced class I HDAC activity and expression, and lowered EZH2 and H3K27me 3 levels in PCa cells, suggesting an epigenetic basis for their effects[90].

Clinical trials

Numerous clinical trials are underway to analyze the beneficial effects of natural products such as catechins including EGCG in inhibiting the growth and development of PCa. For instance, a clinical trial was conducted on 26 men with positive prostate biopsies and scheduled for radical prostatectomy to analyze the protective efficacy of Polyphenon E (PolyE) in PCa patients[85]. The men were supplemented with daily doses of PolyE containing EGCG and other catechins. Their serum biomarkers including hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF)-I, IGF binding protein-3 (IGFBP-3), and prostate-specific antigen (PSA) were analyzed before initiation of the drug study and on the day of prostatectomy in these men and a significant decrease in all these biomarkers with no elevation of liver enzymes was observed during the study. Further, decrease in HGF and VEGF was confirmed in prostate cancer-associated fibroblasts *in vitro*, thereby suggesting the potential role for PolyE in the treatment or prevention of prostate cancer. A similar placebo-controlled, randomized clinical trial of PolyE, a proprietary mixture containing 400 mg EGCG, conducted on 97 men with high-grade prostatic intraepithelial neoplasia (HGPIN) and and/or atypical small acinar proliferation (ASAP) showed a decrease in serum prostate-specific antigen (PSA) on the PolyE arm. However, EGCG was accumulated in plasma and was well tolerated but did not reduce the likelihood of prostate cancer in men with baseline HGPIN or ASAP[104]. In similar lines, in clinical trials of PolyE performed on 97 men with HGPIN and ASAP, so as to analyse the safety of one-year administration of green tea catechins[105], the authors reported accumulation of EGCG in the plasma was well tolerated and did not produce treatment related adverse effects in men.

In another clinical trial by Lane et al[98], the dietary intervention in men at increased risk of PCa was analyzed through randomized Placebo-controlled trial of green tea catechins and lycopene. 569 men with PSA level of 2.0-2.95 ng/mL or 3.0-19.95 ng/mL with negative prostate biopsies were given daily green tea and lycopene: green tea drink (3 cups, unblinded) or capsules (blinded, 600 mg EGCG or placebo) and lycopene-rich foods (unblinded) or capsules (blinded, 15 mg lycopene or placebo) for 6 months. Mean lycopene was observed to be 1.28 times higher in the lycopene capsule group and 1.42 times higher in the lycopene-enriched diet group compared with placebo capsules. Also, EGCG was 10.7 nmol/L higher in the active capsule group and 20.0 nmol/L higher in the green tea drink group compared with placebo capsules. They further suggested the feasibility of a chemoprevention clinical trial.

Further some of the clinical trials have shown the modulation in the bioavailability of catechins when combined with other dietary components. The clinical trial in 31 men with prostate cancer demonstrated the enhanced bioavailability of GT polyphenols (GTPs) and reduced methylation activity with the chronic consumption of green tea extract (GTE) along with quercetin for four weeks before prostatectomy. 14-fold, 12-fold and 4.5-fold increase in quercetin was found in plasma, urine, and prostate tissue, respectively, in the GT + Q compared to the GT + placebo (PL)-group. Also, an increased plasma EGC was observed in the GT + Q in comparison to the GT + PL-group[106]. Wang et al[107], studied the metabolism and bioactivity of green tea polyphenols in men with clinically localized prostate cancer supplemented with green tea polyphenols for 3 to 6 weeks before undergoing radical prostatectomy. 4''-O-methyl EGCG (4''-MeEGCG) and EGCG were observed in comparable amounts, while as ECG was found in lower amounts in prostatectomy tissue. From 50% to 60% of both EGC and epicatechin were present in methylated form in the urine samples of men consuming green tea. Additionally, LNCaP prostate cancer cells incubated with EGCG, were able to methylate EGCG to 4''-MeEGCG and there was significant decrease in the capacity of 4''-MeEGCG to inhibit proliferation and NF-kappaB activation and induce apoptosis in LNCaP cells. Through these clinical trials, the authors suggested the modulation of preventive effects of EGCG based on the methylation status and genetic polymorphism of catechol O-methyl transferase.

CONCLUSIONS

While definitive conclusions about the precise molecular mechanisms by which EGCG operates in PCa are currently elusive, its pivotal role in influencing various molecular pathways, including apoptosis, the AKT pathway, and cell cycle regulation, remains indisputable. The challenge lies in effectively demonstrating EGCG's anti-cancer efficacy in both *in vivo* models and human cancer cell lines, as the majority of the mentioned studies focus on cancer cell lines. Additionally, the potential benefits of combining EGCG with other natural compounds and therapeutic agents shouldn't be disregarded, given its potential to hinder cancer cell proliferation as evident from clinical trials. Furthermore, enhancing EGCG's bioavailability through its integration with other dietary components shows promise. To advance our understanding, future studies should meticulously investigate the intricate molecular mechanisms through which EGCG, either alone or in synergy with other therapeutic agents, effectively restrains the growth and progression of PCa. However, the primary hindrance to establishing EGCG as a potential candidate for cancer prevention and treatment remains the translation of laboratory findings from animal studies to human subjects.

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Author's contributions:
SK Dhatwalia and M. Kumar designed the study and co-authored the manuscript. S Verma and S Rawat extracted the data from the studies. M. Kumar, S Verma and SK Dhatwalia wrote the manuscript. SK Dhatwalia and S Rawat edited the manuscript. All authors read and approved the final manuscript.

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