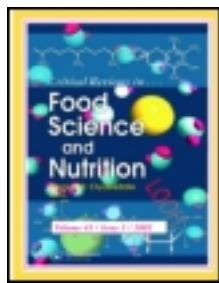


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Critical Reviews in Food Science and Nutrition

Publication details, including instructions for authors and subscription information:

<http://www.tandfonline.com/loi/bfsn20>

Green tea and anticancer perspectives: Updates from last decade

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Accepted author version posted online: 20 Sep 2013.

To cite this article: Critical Reviews in Food Science and Nutrition (2013): Green tea and anticancer perspectives: Updates from last decade, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2012.680205

To link to this article: <http://dx.doi.org/10.1080/10408398.2012.680205>

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Green tea and anticancer perspectives: Updates from last decade

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Abstract

Green tea is the most widely consumed beverage besides water and has attained significant attention owing to health benefits against array of maladies e.g. obesity, diabetes mellitus, cardiovascular disorders, and cancer insurgence. The major bioactive molecules are epigallocatechin-3-gallate (EGCG), epicatechin, epicatechin-3-gallate, epigallocatechin, etc. The anti-carcinogenic and anti-mutagenic activities of green tea were highlighted some years ago. Several cohort studies and controlled randomized trials suggested the inverse association of green tea consumption and cancer prevalence. Cell culture and animal studies depicted the mechanisms of green tea to control cancer insurgence i.e. induction of apoptosis to control cell growth arrest, altered expression of cell cycle regulatory proteins, activation of killer caspases, and suppression of nuclear factor kappa-B activation. It acts as carcinoma blocker by modulating the signal transduction pathways involved in cell proliferation, transformation, inflammation, and metastasis. However, results generated from some research interventions conducted in different groups like smokers & non-smokers, etc. contradicted with aforementioned anticancer perspectives. In this review paper, anticancer perspectives of green tea and its components have been described. Recent findings and literature have been surfed and arguments are presented to clarify the ambiguities regarding anticancer perspectives of green tea and its component especially against colon, skin, lung, prostate, and breast cancer. The heading of discussion and future trends is limelight of the manuscript. The compiled manuscript provides new avenues for researchers to be explored in relation to green tea and its bioactive components.

Keywords: Green tea; anticancer; antimutagenic; metastasis; apoptosis

Background and Introduction

In the domain of nutrition, concepts of functional & nutraceutical foods are gaining immense popularity and functional ingredients present in them are important against various ailments. In recent years, the diversification of dietary habits to include healthy foods have been recognized as alternative to medicines or drugs (Butt and Sultan, 2009). Diet-based strategies often employ plants and their bioactive molecules (dietary phytochemicals) owing to their health promoting potential (Butt et al, 2012). Overall, it has been assumed that functional/nutraceutical foods may improve human health by lowering the risks for certain diseases (Ares et al., 2009). Array of phytochemicals rich plants hold biological activities, e.g. tea, garlic, ginger, cruciferous vegetables, berries, etc. Amongst, tea is one of the most widely studied natural product (Butt and Sultan, 2009). Green tea technically refers to the product manufactured from fresh tea leaves by steaming or drying to limit the oxidation of the polyphenolic components, especially flavanols (Wang et al., 2000; Yang and Landau, 2000; Vinson et al., 2004; Shaheen et al., 2006; Khan et al., 2009; Sasazuki et al., 2012).

Green tea has engrossed significant attention, both in scientific and consumer communities owing to its health benefits against variety of maladies ranging from weight loss to cancer (Hara, 2006; Morita et al., 2009; Shimizu et al., 2012). The chemical composition of tea varies with climate, season, agricultural practices, variety, age and position of the leaf (Lin et al., 2003). The proximate composition of different dry green

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tea leaves includes moisture, protein, lipid, sugar, fiber, ash and caffeine ranging from 2.2-5.0, 18.2-30.7, 3.5-5.3, 28.6-39.2, 10-19.5, 5.4-7.4 and 1.9-3.5g/100 g, respectively (Chee and Juneja, 1997). Mineral composition of green tea varies widely and levels of Zn, Mn, Fe, Ca, Na and K on dry weight basis ranged from 2.1-3.5, 66-160, 14-35, 36-54, 3.8-11.7 and 1190-1699mg/100g, respectively (Fernandez-Caceres et al., 2001). In addition, green tea also contains alkaloids, such as caffeine, theobromine and theophylline, which constitute minor portion of solids and vary from 0.6 to 28.6 mg/g (Shaheen et al., 2006, and Friedman et al., 2006).

Polyphenols are the main bioactive constituents of green tea (Higdon and Frei, 2003; Shaheen et al., 2006), and their content varies considerably among different green teas. Asghar and Masood, (2008) reported that total polyphenol content (TPC) of green tea was about 31g/100g. Recently, Soysal (2009) stated that TPC of green tea was about 12 mg/g. Moreover, Anesini et al. (2008) mentioned that TPC in green tea varied from 14to 21g/ 100 g. Majority of green tea polyphenols are flavanols commonly recognized as catechins (Balentine et al., 1997). The major green tea catechins are epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG) and epicatechin (EC). Among them, EGCG is the most abundant one accounted for more than 50% of total polyphenols (Bettuzzi et al., 2006). Generally, catechins are low molecular weight, colorless and water-soluble compounds with bitter and astringent taste (Wang et al.,

2000). The structures of catechins along with their molecular formula/weights and IUPAC names are presented in Table 1.

Insert Table 1 here

Health claims of green tea are attributed to its polyphenolic fractions known as catechins. In toto, green tea catechins possess anti-obesity, anti-hypercholesterolemic, anti-hyperglycemic and anticancer properties (Kanwar et al., 2012). In green tea, catechins are present in higher amounts than those in black or oolong tea due to the processing differences (Scalbert et al., 2005; Zaveri, 2006; Yilmaz, 2006). The literature pertaining to anticancer effects of the green tea is reviewed herein.

I. Green tea catechins and malignancy

Nowadays, cancer is one of the leading causes of human mortality, and chemoprevention is a promising strategy. Chemoprevention involves usage of synthetic and natural compounds that may block initiation, promotion, and progression of cancerous cells. In this regard, bioactive molecules present in green tea plant have attracted the attention of researchers owing to efficacy in multiple sites, negligible side effects, low toxicity, easy oral consumption, cheapness, and human acceptance (Lin et al., 1999, Gonzalez, 2006). Much of the cancer chemopreventive properties of green tea are mediated by EGCG that induces apoptosis and promotes cell growth arrest in cancer cells. EGCG modulates the signal transduction pathways involved in cell proliferation, transformation, inflammation, apoptosis and metastasis (Khan et al., 2006;

Na and Surh, 2006; Huang et al., 2008; Hu et al., 2010). The cancer-preventive effects of green tea are widely supported by epidemiological, animal and clinical studies revealing that treatment with green tea may inhibit tumor incidence and multiplicity in different organ sites such as skin, lung, liver, stomach, mammary gland and colon. The detailed discussion is provided herein.

A. Colon cancer

Colon cancer is the second leading cause of cancer-related deaths in the U.S. Epidemiological studies confirmed converse correlation between utilization of green tea and colon insurgence. Numerous population-based studies in Japan and China where people regularly consume green tea revealed inverse association of green tea with colon cancer(Khatiwada et al., 2006; Xu et al., 2010). The modes of actions for green tea include activation of AMPK, decreased COX-2 expression & prostaglandin, and induction of apoptotic markers such as p53 and PARP cleavage (Shimizu et al., 2005; Park et al., 2009). The activation of AMPK along with reduced expression of VEGF (vascular endothelial growth factor) and glucose transporter (Glut-1) further supports the regulatory role of AMPK in COX-2 expression in EGCG-treated cancer cells (HWang et al., 2007). These effects may also explain the ability of EGCG to inhibit activation of other membrane-associated RTKs that play critical role in the anticancer effects (Adachi et al., 2007). EGCG also inhibits the binding of EGF to the EGFR that results in anticancer perspectives (Adachi et al., 2007). Phosphorylation of EGFR at

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serine 1046/1047 via activation of p38 MAPK also plays a pivotal role in EGCG-induced down-regulation of EGFR (Adachi et al., 2009). Recently, Lee et al., (2010a) presented some more evidences that EGCG-induced apoptotic cell death is accompanied by a change in the cell cycle without altering the caspase activation. The increased levels of p53, Bax, were escorted with decreased Bcl-2 and Bid protein levels. The contributing factor could also cytoplasmic release of cytochrome c accompanied by a decreased mitochondrial membrane potential that upregulated translocation of apoptosis-inducing factor (AIF) and endonuclease G (EndoG) in human laryngeal epidermoid carcinoma Hep2 cells. EGCG also enhanced pro-matrix metalloproteinase (MMP)-7 in HT-29 human colon cancer cells via spontaneous superoxide generation. Green tea can decrease early biomarker of carcinogenesis that includes β -catenin and cyclin D1 (Issa et al., 2007) The molecular targets for green tea catechins also include Ras and activator protein (AP)-1, elements of the mitogen-activated protein kinase (MAPK) signaling pathway, and inhibition of c-Jun N-terminal kinase (JNK) pathway (Kim et al., 2007; Li et al., 2010a). EGCG exerts its anti-inflammatory and anti-folate action by enhancing activity of adenosine receptors thus inhibiting NF- κ B activity, phosphorylation of I κ B α and Akt in colon cancer cells (Navarro-Perán et al., 2008).

Modulation of NF- κ B activation is also one of the effective mechanism that is helpful in controlling the inflammatory response and allied discrepancies especially cancer insurgence (Navarro-Perán et al., 2008). Previously, Peng et al., (2006) reported

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that EGCG down regulated the ERK1/2 and Akt pathways in colon cancer cells. The transmembrane protein-tyrosine phosphatase DEP-1 (density-enhanced phosphatase) upregulation results in inhibition of cell growth and cancerous cell invasions (Jeong et al., 2004). Moreover, EGCG also results in momentary improvement in the expression of TGF- β 2, an inducer of IGFBP-3 expression (Shimizu et al., 2005). The similar effects were also observed for green tea catechins as retinoid X receptor (RXR) α expression was reduced along with aforementioned mechanism (Xiao et al., 2007a). Previously, Jia and Han, (2001) investigated the effect of green tea on 1,2-dimethylhydrazine (DMH)-induced aberrant crypt foci (ACF) formation and concluded that green tea drinking inhibited ACF formation in rodents, and such effects may be related to the suppression of cell proliferation in the intestinal crypts (Zhang and Shen, 1997). Larsen and Dashwood, (2009) reported that EGCG suppressed the activation of Met in the presence of HGF and effects were not influenced from the production of H₂O₂ in cell culture media.

The suppression of TROP-2 is important as it acts as biomarker of carcinogenesis. In this regard, Sukhthankar et al., (2010a) provided evidences that green tea suppresses the expression of TROP-2 in colorectal cancer. EGCG @ 5 μ /ml up-regulated the expression of nuclear factor erythroid 2 related factor 2 (Nrf2) that was positively correlated with increased level of uridine 5'-diphosphate-glucuronosyltransferase (UGT) in cells (Zhang et al., 2009a; Sukhthankar et al., 2010b). Earlier, Yuan et al., (2007) suggested the same

mechanism of action for the prevention of liver and pulmonary metastases of orthotopic colon cancer in nude mice. DNA topoisomerases I and II are concerned with metabolism and structure of DNA. Green tea and its catechins repress growth and development of cancer cells without any effect on normal cells. This topoisomerase inhibiting activity of green tea therefore could be helpful strategy for treatment of colon cancer (Berger et al., 2001). Green tea catechins in combination with curcumin shows better colon cancer chemo-preventive activity in induced rats by inhibiting the total number of colorectal aberrant crypt foci (ACF), reducing the proliferation index and improving the apoptotic index (Khatiwada et al., 2006; Xu et al., 2010).

B. Breast cancer

Breast cancer has become the second leading cause of cancer-related deaths worldwide and its frequency is increasing over the globe. Several cell culture, animal modeling, and cohort studies have explored anticancer effects of green tea. Green tea polyphenols possess the ability to amend epigenetic events which play role in prevention and treatment of breast cancer (Khan et al., 2012). Green tea catechins and its principal constituent EGCG are effective in suppressing the proliferation of MDA-MB-231 (a highly invasive estrogen receptor- negative breast cancer cell line). Thangapazham et al., (2007) elaborated that arresting the cell cycle at G1 phase, along with reduced expression of Cyclin D & E, CDK 4 & 1, and PCNA are other contributing factors. Furthermore, catechins @ 0.5% can impede initiation of tumor and its growth upto

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40% through suppression of ductal epithelial cells and tumors proliferation thus preventing angiogenesis (Leong et al., 2008).

Recently, Roy et al., (2010a) examined the inhibitory effect of green tea catechins against 7, 12-dimethylbenz (a) anthracene (DMBA) induced breast cancer tumors in Female Wistar rats. The green tea catechins successfully inhibited number of tumors (92%) through scavenging ROS. The inhibition was observed to be mediated by inhibition of cyclooxygenase-2 (Cox-2) and inactivation of phosphorylated forms of NF-kappaB & Akt. The resulting decrease in carcinogenesis is further supported by the altered miRNA regulation of potential oncogenes and tumor-suppressor genes (Fix et al., 2010). Epigallocatechin (EGC) represses the expansion of breast cancer cell lines (MCF-7 and MDA-MB-231) through apoptosis that might be linked to improved ratio of Bcl-2/Bax level. However, EGCG can also activate the caspase-3 & 9, mitochondrial membrane potential, and JNK signaling pathways (Zhao et al., 2006; Hsuuw `and Chan, 2007; Stuart et al., 2007). In another study, EGCG suppressed cell viability and induce apoptosis by down-regulation of telomerase and inhibited angiogenesis by reducing expression of vascular endothelial growth factor (VEGF) in a dose-dependent manner (Sartippour et al., 2002; Mittal et al., 2004). EGC and EGCG might inhibit metastasis of breast cancer cells through inhibition of heregulin-beta1 (HRG)-induced migration/invasion of MCF-7 cells. The suppression of HRG-stimulated activation of epidermal growth factor receptor-related protein B2 (ErbB2)/ErbB3/protein kinase B

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(Akt), whereas EGC did so through pathways including the disruption of the HRG-stimulated activation of ErbB2/ErbB3 but not Akt (Kushima et al., 2009). EGCG decreased the migratory and invasive potential of MCF-7 cells with a concomitant down-regulation of vasodilator-stimulated phosphoprotein (VASP) expression via Rac1 pathway (Zhang et al., 2009b). Green tea catechins represses the chronically induced cellular carcinogenesis by jamming increase in reactive oxygen species, ERK commencement, cell proliferation and DNA damage (Sakata et al., 2011; Rathore et al., 2012).

Lipogenesis is critical in cancer cells as enzyme fatty acid synthase (FASN) regulating lipogenesis is articulated in breast cancer. The green tea catechins especially EGCG prevented FASN activity in research study conducted by Puig et al., (2008). Likewise, status of estrogen receptor- α (ER α) is critical to the clinical prognosis and therapeutic approach in breast cancer. Combination studies using EGCG with the histone deacetylase (HDAC) inhibitor, trichostatin A (TSA), revealed a synergistic effect of reactivation of ER α expression in ER α -negative breast cancer cells (Li et al., 2010). EGCG @ 50 μ g/ml could stop MCF-7Tam cell growth and in vitro invasion through down-regulation of EGFR and other molecules including ERK (extracellular regulated kinase), phospho-ERK p42/44, MMP-2 & -9, and EMMPRIN were significantly reduced (Farabegoli et al., 2010). Earlier, Sen et al., (2009) enumerated that reduced activity of MMP-2 due to reduced protein & mRNA expression can be possible route to control

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breast cancer as a function of EGCG. The reduced expression of focal adhesion kinase (FAK), MMP, nuclear factor-kappa B (NF- κ B), vascular-endothelial growth factor (VEGF), and adhesion of MCF-7 cells to ECM, fibronectin and vitronectin are also possible mechanisms for anticancer perspectives of green tea catechins. Combinational administration of flavonoids capable of suppressing HSP70 and GRP78 such as quercetin and EGCG might represent a novel approach for cancer therapy or chemoprevention. The application of EGCG is effective in suppressing GRP78 induction through down-regulation of heat shock protein 70 (HSP70) thus decreasing the cell proliferation (Tran et al., 2010). The down-regulation of HSP70 leads to the induction of unfolded protein response (UPR). Water-soluble oligomeric epicatechins surpass EGCG in stability, selectivity and efficacy at lower doses (Nagarajan et al., 2008). Methylated (-)-EGCG is less bioactive and supports the notion that catechol-Omicron-methyltransferase (COMT) inhibition may increase the anti-cancer properties of tea polyphenols (Landis-Piwowar et al., 2010).

Moreover, daily consumption of three or more cups of green tea prevents risk of reappearance of breast cancer in woman (Inoue et al., 2001; Iwasaki et al., 2010a). However, due to substantial difference in levels of estrogens between premenopausal and postmenopausal women, the relationship between tea consumption and breast cancer risk may depend on menopausal status. The concepts are little different as estrogen therapy to cure problems related to menopause can enhance the risk of breast

cancer. However, the women without uterus usually are at lower risk due to differences in their metabolisms. It is therefore recommended that lower dose should be used for short duration. Adding progestin in the therapy may reduce the the risk of colorectal cancer but risk of breast cancer can be increased. Therefore, an integrated may be adopted considering the status of women with special reference to their age, menopause status, etc. for designing an optimum drug & nutrition strategy for getting maximum benefits.

C. Lung cancer

Lung cancer is one of the most common cancers in the world and leading cause of cancer death in developed countries. The cancerous growth in lungs are bronchogenic lesions that are further split into two broader categories i.e. small cell lung carcinoma (SCLC) versus non-small cell lung carcinoma (NSCLC). These types are treated differently as SCLC can response bettwe to responds better to chemicals/botanicals and radiations. On the other hand, surgery is most suitable option for treating NSCLC. The activation of signaling pathways (Raf-1 & mitogen-activated (MAP) kinase) are also important in human SCLC. Whereas, human pulmonary adenocarcinomas of Clara cell lineage are regulated by a beta-adrenergic pathway that include the activation of cyclic adenosine 3',5'-monophosphate (cAMP) and the arachidonic acid (AA) cascade (Schuller et al., 2004). Green tea inhibits lung tumor development in A/J mice treated with 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The mode of action

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include inhibition of 8-hydroxydeoxyguanosine (8-OH-dG) that acts as marker of oxidative DNA damage (Chung, 1999). Lungs cancer introduced by injection of 3,4-benzopyrene was decreased by green tea through enhanced expression of p53 gene but reduced activity of bcl-2 (Gu et al., 2009). Previously, Gu et al., (2008) observed the similar effects in cell culture studies. Green tea exerts its apoptotic effect on human H460 cell line through both P(53) and Bcl-2 (Hessien et al., 2011).

In cell culture studies, the growth of viable H1299 cells was dose dependently reduced by EGCG interaction with G3BP1 and Ras-GTPase activating proteins thus suppressing the activation of Ras in shMock-transfected H1299 cells (Shim et al., 2010). EGCG with IC₅₀ value of 70 μM resulted in 50-60% reduced telomerase activity along with reduction in caspases 3 (50%) & 9 (70%) activities. EGCG further blocked cell-cycle arrest in S phase (Sadava et al., 2007). Previously, Okabe et al., (2001) presented the effects of (-)-epigallocatechin gallate (EGCG) on expression of 588 genes in human lung cancer cell line PC-9 cells. They observed that EGCG-treated cells induced down-regulated expression of 12 genes including NF-kappaB inducing kinase (NIK), death-associated protein kinase 1 (DAPK 1), rhoB, and tyrosine-protein kinase (SKY). In comparison, EGCG treatment enhanced the expression of four other genes including retinoic-acid receptor-α1. Based on previous evidences, NIK gene expression is of prime importance for anticancer perspectives of green tea and its bioactive molecules (Arts, 2008). Lai et al., (2004) attributed the inhibition of morphogenesis of endothelial cells in collagen gel

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by EGCG through down-regulation of Ets-1, c-Fos, and c-Jun. The increased percentages of cells in the G2-M phase can be possible mechanism of growth inhibition by EGCG @ 50 μ M & 100 μ M (Okabe et al., 1997). Additionally, EGCG also leads to DNA fragmentation thus blocking cell cycle arrest in S phase (Sadava et al., 2007). Overall, green tea catechins administration hold the potential to reduce the incidence (52%) and multiplicity (63%) of lung adenocarcinoma (Liao et al., 2004).

EGCG and ECG inhibited the growth of A549 cells in a dose-dependent manner attributed to decreased level of hnRNP B1 protein and cell cycle arrest at G2/M phase cells with IC₅₀ values of 29 μ M for EGCG (Lu et al., 2008). Decaffeinated green tea extract Polyphenon E (Poly E) @ 1% in diet reduced the tumor load in animals. However, the effects were more confined to NSCLC (Anderson et al., 2008). Additionally, catechin mixture up-regulates p53 reporter and EGCG was found to be more potent inducer in treated A549 cells (Lu et al., 2006b; Yamauchi et al., 2009). The green tea has been incorporated in nutrients mixtures especially designed for cancerous studies in animal models (Gu et al., 2009; Roomi et al., 2010). According to Deng and Lin (2011) green tea might be strong inhibitor of MMP-2 expression as EGCG (green tea component) conceals the incursion and immigration of highly invasive CL1-5 lung cancer cells. They used the Gelatin zymography, Western blot analysis, and RT-PCR to inspect the effects of EGCG on MMP-2 expression. EGCG not only decreased MMP-2 appearance in CL1-5 cells but also decreased the c-Jun N-terminal kinase (JNK) activity

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leading to oppression of the relocation of transcriptional factors, Sp1, and NF- κ B into the nucleus. Green tea exhibits its anti cancer effect in lung cell lines by increasing miR-210 carried through stabilization of HIF-1 α (Wang et al., 2011). Green tea apoptotic activity is due to lipid raft clustering carried through 67-kDa laminin receptor (67LR). Green tea EGCG stimulates relocation of aSMase to the plasma membrane and phosphorylation of protein kinase C delta (PKC δ) at Ser664 essential for aSMase/ceramide signaling (Tsukamoto et al., 2012).

Intra-pulmonary injection of 3,4-benzopyrene can steadily induce lung carcinoma in rats, and green tea (tea @ 1.2% and GTP @ 0.3%) has preventive effect against lung cancer possibly by regulating expression of some critical genes such as p53 and bcl-2 (Gu et al., 2009). Latterly, Roy et al. (2010b) presented mechanism of chemoprevention that include that cellular signaling pathways e.g. expression of Akt, cyclooxygenase-2, and inactivated nuclear factor-kappa B. In another study, EGCG (4.19mg/kg) decreased tumor multiplicity whereas green tea catechins without EGCG failed to inhibit lung carcinogenesis (Fu et al., 2009). Activation of the c-Met and epidermal growth factor receptors (EGFR) promotes the growth and survival of non-small cell lung cancer (NSCLC) by EGCG (Milligan et al., 2009). EGCG inhibits the activity of many heat shock proteins (Hsp90)-dependent client proteins, including telomerase, several kinases, and the aryl hydrocarbon receptor (Donnelly and Blagg, 2008).

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The combinations of green tea catechins with some other nutrients e.g. curcumin are reported to be more influencing in inhibiting cancerous growth. In one such study, EC enhanced the cancer-preventive activity of EGCG. The combination of curcumin with EC also significantly increased the inhibition of cell growth through apoptosis and expression of GADD153 and GADD45 genes (Saha et al., 2010b). The study carried out by Suganuma et al., (1999) on incorporation of EGCG into human lung cancer cell line (PC-9) indicated that incorporation was significantly enhanced by epicatechin thus resulting in enhanced apoptosis, growth inhibition, and inhibition of TNF- α release in a dose-dependent manner. Previously, green tea extract (GTE) has reported to induce actin remolding that is associated with increased cell adhesion and decreased motility. GTE-induced lamin A/C upregulation resulted in decreased cell motility (Lu et al., 2009).

Mechanisms of green tea for chemoprevention of lung cancer includes antioxidant activity, phase II enzymes induction, inhibition of TNFalpha expression and release, inhibition of cell proliferation and induction of apoptosis. However, inhibition of key protein kinases involved in cell cycle regulation and induction of apoptosis are of prime importance (Clark and You, 2006; Lee et al., 2010b).

D. Prostate cancer

Prostate cancer (PCa) is second only to lung cancer as the cause of cancer-related deaths in American men and is responsible for over 29,000 deaths per year. A large number of

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epidemiological studies suggested that consumption of green tea reduces the risk of prostate cancer (Bettuzzi et al., 2007; Khan et al., 2009; Henning et al., 2012). *In vivo* and *in vitro* trials revealed that green tea encourages apoptosis, restrains progression, and prevents invasion and metastasis of prostate cancer (Connors et al., 2011). In one such study, EGCG suppressed cell proliferation, prostate specific antigen (PSA) expression, and AR transcriptional activity in different LNCaP sub-lines (Chuu et al., 2009). Epigenetic silencing of glutathione-S-transferase pi (GSTP1) is recognized as being a molecular target in human prostate cancer. The green tea catechins @ 1-10 µg/ml caused a dose- and time-dependent re-expression of GSTP1 that might be correlated with DNMT1 inhibition (potential role in DNA methylation) and increased levels of acetylated histones (Pandey et al., 2010). Furthermore, androgen-independent prostate cancer cell line Du145 treated with or without EGCG showed that DNA binding 2 (ID2) was found to be down-regulated by EGCG treatment (Luo et al., 2010). Recently, Nair et al., (2010) studied the changes in gene expression induced by EGCG @ 100 mg/kg. They demonstrated that the effects of EGCG could be mediated via concerted modulation of Nrf2 and AP-1 pathways in the prostate. Additionally, green tea catechins dual potential to alter DNA methylation and chromatin modeling along with low toxicity makes them excellent candidates for the chemoprevention of prostate cancer (Pandey et al., 2010). Previously, Baylin and Herman, (2000) highlighted the importance of molecular processes that mediate methylation changes. They were of the view that understanding of chromatin modeling and gene regulation might present novel

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possibilities for cancer therapy. The degree of DNA methylation can be used as marker to detect the risk of cancer insurgence and indeed monitor the cancer prevention through early diagnostic and prognosis of cancer.

The HGF/c-Met pathway is another signaling pathway responsible for invasion and metastasis. The EGCG inhibited the PI3-kinase and MAPK expressionm through prevention of phosphorylation of tyrosines 1234/1235 in the kinase domain of the c-Met receptor (Duhon et al., 2010). The inhibition of sphingosine kinase-1/sphingosine 1-phosphate (SphK1/S1P) pathway by EGCG is another potential mechanism associated with cancer promotion & progression thus decreasing tumor volume and metastasis (Brizuela et al., 2010). Albrecht et al., (2008) attributed the activation of extracellular signal-regulated kinase (ERK1/2) pathway for anti-proliferative effects of EGCG in the PC-3 prostate cancer cell line. However, ERK1/2 activation is dependent on phosphoinositide-3 kinase (PI3K). Green tea catechins including EGCG may performs its chemopreventive action by increasing expression of CLU gene. Green tea catechins inhibit growth of human prostate cancer DU145 cells and induce apoptosis by enhancing formation of reactive oxygen species and mitochondrial depolarization (O'Sullivan et al., 2008).

Green tea polyphenols at concentration of 10-80 µg/ml subdued I HDAC enzyme activity and its protein expression in human prostate cancer (LNCaP and PC-3) cells (Thakur et al., 2012). According to Adhami et al., (2004) IGF-I/IGFBP-3 signaling

pathway is prime pathway for green tea polyphenol-mediated inhibition of prostate cancer through inhibition of angiogenesis and metastasis. The treatment with tea ingredients results in (i) significant inhibition in growth of implanted prostate tumors, (ii) reduction in the level of serum prostate specific antigen, (iii) induction of apoptosis accompanied with upregulation in Bax and decrease in Bcl-2 proteins, (iv) decrease in the level of VEGF protein, inhibition COX-2 without affecting COX-1 expression (Hussain et al., 2005; Siddique et al., 2006). EGCG mediated its anticancer effects through cell cycle arrest at G0/G1-phase, induction of apoptosis through increased p53 expression, and generation of cyclin kinase inhibitor WAF1/p21.

One mechanism involved in anticancer perspective of green tea is suppression of DNA synthesis marker mini-chromosome maintenance protein 7 (MCM7). Green tea catechins suppressed MCM7 and MCM7 gene expression (McCarthy et al., 2007). Later, Siddiqui et al., (2009) attributed anticancer potential of green tea catechins (0.1% as drinking medium) to inhibition of NFkappaB signaling that further shift balance between Bax & Bcl2 proteins. The green tea catechins further decreased the expression of TNF- α , IL-6, and IL-1 β (Hsu et al., 2010).

E. Skin cancer

Skin is prime organ of the human body that protects body from invading pathogens. However, patients with skin cancers are increasing at alarming rate. The skin cancer is further split up into melanoma, basal cell carcinomas, squamous cell carcinomas,

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kaposi's sarcoma, cutaneous, and T-cell lymphoma & melanoma. The classification of skin cancer is due to differences in pathogenesis and type of cells and layers of skin e.g. melanoma is cancer of pigmented cells while basal cell carcinomas is slow growing and occurs in skin exposed to sunlight and lowest layer of the epidermis is mainly affected. Experimental studies involving animals, green tea catechins application results in lower tumor body burden such as decrease in total number of tumors per group, number of tumors per animal, tumor volume per mouse and average tumor size (Butt and Sultan, 2009; Khan and Mukhtar, 2010).

Green tea possesses ability to prevent UV-initiated skin irritation, propagation, DNA injures and dysregulation of significant signaling pathways. The research interventions carried out in early nineties focused on topical application of green tea catechins. 12-O-tetradecanoylphorbol 13-acetate (TPA) was commonly employed as tumor promoter in two-stage skin tumorigenesis protocols. The results were quite conclusive that green tea catechins may provide significant protection against skin tumorigenesis in SENCAR, CD-1, and Balb/C mice models (Wang et al., 1989; Mukhtar et al., 1994, Katiyar et al., 1992). Furthermore, intra-peritoneal GTC or EGCG application also reported to inhibit tumor growth thus reducing the extent of established skin cancer lesions. Epidermal aryl hydrocarbon hydroxylase activity and epidermal enzyme-mediated binding of BP and DMBA to DNA was inhibited by these polyphenols (Wang et al., 1989). The 0.1% GTC in drinking water controlled skin carcinogenesis induced by UVB radiation

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exposure (Wang et al., 1991). More recently, oral administration of GTC (2g/L) reduced UVB-induced tumor incidence (35%), tumor multiplicity (63%), and tumor growth by 55% (Meeran et al., 2009).

GTPs and EGCG prevents UVB-induced skin tumor development and this prevention is mediated involving different mechanisms (Meeran et al., 2006), (i) reduced expression of matrix metalloproteinases (MMP-2 & MMP-9), (ii) reduced expressions of CD31 and vascular endothelial growth factor, (iii) more cytotoxic CD8(+) T cells, (iv) activation of caspase-3, (v) reduced levels of inflammatory responses (cyclooxygenase-2, prostaglandin, proliferating cell nuclear antigen, and cyclin D1), (vi) pro-inflammatory cytokines including TNF- α , IL-6, & IL-1 β , (vii) IL-12-dependent DNA repair, and (viii) nucleotide excision repair mechanism. The inhibition of UV-induced immunosuppression and modulation of indices of angiogenesis are also important in anticancer perspectives of green tea and its functional ingredients (Mantena et al., 2005; Katiyar et al., 2007; Meeran et al., 2009). In this regard, Roy et al., (2009) further studied the mitochondrial pathway of apoptosis were mediated partially from upregulation of p53 and Bax, whilst decreasing the expression of Bcl-2. Consequently, tea polyphenols supplementation resulted in release of cytochrome c, caspases activation, and increase in apoptotic protease activating factor and poly (ADP-ribose) polymerase cleavage thus inducing apoptosis. Recently, Balasubramanian et al., (2010) highlighted that EGCG influenced polycomb group (PcG) proteins mediated epigenetic regulatory mechanism.

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The changes in P_cG protein expression is associated with reduced expression of key proteins that enhance progression through the cell cycle and increased expression of proteins that inhibit cell cycle progression (p21 and p27). The induction of apoptosis is also associated with activation of caspase 9, 8 and 3 cleavage and modulation of Bax and Bcl-xL proteins.

UVB-induced DNA damage (cyclobutane pyrimidine dimers) can be cured using the bioactive molecules present in green tea (Meeran et al., 2009). The formation of cyclobutane pyrimidine dimmers results in immunosuppression that further leads to initiation of skin cancer. The induction of apoptosis in skin layers owing to UVB exposure is inhibited through catechins application and effects were mediated through enhanced expression of IL-12 (Schwarz et al., 2008). Katiyar, (2010) further confirmed the findings as he suggested that topical application or oral administration of green tea through drinking water prevents UVB-induced skin tumor development in animal model (Hsu et al., 2007).

However, green tea holds skin cancer preventive effects when applied topically before UV exposure but application of EGCG is useless after UV exposure (Sevin et al., 2007). Regular intake of EGCG further strengthens the skin's tolerance by increasing minimal erythema dose (MED) thus preventing UV-induced perturbation of epidermal barrier function and skin damage (Jeon et al., 2009).

F. Cervical cancer

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Cervical cancer is the second most common cancer in women resulting in causalities worldwide. Green tea catechins and EGCG are effective in inhibiting cervical cancer. The mode of actions includes induction apoptosis that is well correlated with increased expression of apoptosis-mediating proteins (p53 & p21), whilst HPV-E7 protein expression was decreased (Yokoyama et al., 2008; Zou et al., 2010).

The green tea polyphenols (GTP) holds the ability to inhibit proliferation of cells which is associated with an increase in the G2/M phase. Additionally, GTP induces apoptosis in treated SiHa (human cervical cancer) cells through reducing mitochondrial membrane potential, and increasing the levels of membrane phosphatidylserine residues (Singh et al., 2010). EGCG treatment leads to DNA ladder formation in immortalized HPV 18- immortalized endocervical, and HPV 18-immortalized ectocervical cells (Qiao et al., 2009). EGCG dose dependently inhibited the growth of CaSki (HPV16 positive) and HeLa (HPV18 positive) cells by induction of apoptosis and cell cycle arrest. In cervical carcinogenesis, early stage activation of telomerase results in instigation and growth of cervical lesions (Zheng et al., 1997) which is prohibited by EGCG inhibition of telomerase activity (Yokoyama et al., 2004). In another study, green tea ethanolic extract with higher amount of EGCG (62.5– 250 µg/ml) prevented proliferation of human cervical adenocarcinoma HeLa cell in dose dependent manner (Li et al., 2008b). Al-Hazzani and Alshatwi (2011) investigated the CH (Catechin hydrate) for its cytotoxic and growth-inhibition possessions. Results showed that 196.07

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µg/mL of CH lead to 50% reticence of SiHa human cervical cancer cells. Actually CH caused the increase of caspase-3, -8, and -9 which may be responsible for the stimulation of apoptosis. They further used the Dead End terminal transferase-mediated dUTP-digoxigenin-end labeling (TUNEL) assay which confirmed the ability of green tea CH to inhibit the cervical cancer.

The combination of EGCG and vitamin A increases the expression of the 67 LR that promotes anticancer activity of EGCG. However, the selection of dose is very important as it has been observed that EGCG @ 35 µM inhibited the growth of cervical cancer cell lines but unable to induce apoptosis. Consequently, the increased dose of EGCG (100 µM) resulted in apoptotic lesions after 24 hours of treatment. Thus, EGCG provides an additional option for a new and potential drug approach for cervical cancer patients (Ahn et al., 2003).

G. Bladder cancer

In the recent era, the prevalence of bladder cancer is increasing over the world. During 1985 to 2006, the patients registered increased by 50% only in USA. The progression of bladder cancer occurs due to over-expression of AKT kinases leading to endurance of tumor cells and increased resistance to apoptosis (Philips et al., 2009). Qin et al., (2007) worked on T24 human bladder cancer cell line and showed that repressed cellular proliferation and cell viability by EGCG is dose and time dependent. EGCG hinders activation of phosphatidylinositol 30-kinase/Akt which leads to modulation of Bcl-2

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family proteins resulting in enhanced apoptosis of T24 cells. The animal modeling using N-butyl-N-(4-hydroxybutyl)-nitrosamine (BBN) induced bladder cancer, the treatment with green tea leaves may be suitable for prevention of BBN-induced urinary bladder tumors when given before the carcinogen (Sato and Matsushima, 2003). In another study, Kemberling et al., (2003) evaluated the EGCG as an intravesical agent for the prevention of transitional cell tumor implantation. The EGCG injection inhibited the tumor growth in time & dose dependent responses and effects were mediated through down-regulating the cyclin D1, cyclin-dependent kinase 4/6 and retinoblastoma protein machinery for regulating cell-cycle progression (Chen et al., 2004).

Green tea extract induced annexin-I expression that plays a key role in regulating actin remodeling and thus decreased annexin-I expression is a common event in early stage of bladder cancer (Xiao et al., 2007b). Green tea catechins inhibit tumor growth and invasion in mice with established bladder cancer, at least in part through the regulation of angiogenesis (Sagara et al., 2010). Rieger-Christ et al., (2007) further explained the mechanisms behind the anticancer effects of EGCG against bladder cancer. They reported that EGCG inhibited the *in vitro* growth of invasive bladder carcinoma cells with an IC₅₀ range of 70-87 μM. However, the lower dose of EGCG (20μM), migratory potential of bladder carcinoma cells decreased with concomitant activation of p42/44 MAPK & STAT3 and inactivation of Akt. Additionally, EGCG down-regulated N-cadherin in a dose-dependent manner as reduction in N-cadherin expression paralleled

declining migratory potential. They further observed continuous administration of EGCG to mice inhibited tumor growth *in vivo* indicating a possible preventative role for green tea in bladder cancer.

H. Oral cancer

The catechins and its components are effective in inducing apoptosis in the oral cancer cells thus showing the effectiveness of green tea against oral carcinoma (Babich et al., 2005). Green tea, most widely consumed beverage has received considerable attention because of beneficial effects in oral cancer chemoprevention with regard to the multiple molecular mechanisms proposed in various in vitro, in vivo, and clinical trials (Lee and Choi , 2011). Ho et al., (2007) suggested that EGCG could inhibit the invasion and migration of human oral cancer cells. The effects are ought to decreased productions of MMP-2, MMP-9, and urokinase plasminogen activator (uPA). It is for further information for the readers that EGCG can significantly suppress cancer cell invasion by decreasing the number of invasive foci. Mohan et al., (2007) also investigated the anticancer effects of green tea polyphenols and observed dose dependent inhibition of CAL-27 cells. The inhibition was mediate by apoptosis via generation of reactive oxygen species and modulating Bcl-2/Bax ratio. These effects further led to induce mitochondrial permeability transition with consequent activation of caspase-3. The inhibition of cyclin-dependent kinase is another mechanism that can reverse the onset of tumorigenesis through controlling cell growth, differentiation, and apoptosis. In this

regard, EGCG up-regulates p21WAF1 that results in growth arrest and caspase 3-mediated apoptosis (Hsu et al., 2005). Furthermore, EGCG suppresses the induction of indoleamide 2,3-dioxygenase (IDO) at transcriptional level through blocking IFN-gamma-induced JAK-PKC-delta-STAT1 signaling pathway (Cheng et al., 2010). Likewise, the expression of RECK (a novel tumour suppressor gene) that negatively regulates matrix metalloproteinases (MMPs) and inhibits tumour invasion, angiogenesis and metastasis. EGCG plays a key role in suppressing cell invasion possibly through demethylation effect on MMP inhibitors (Kato et al., 2008).

II. Discussion and future trends

The cancer insurgence is dependent upon many factors that can be further categorized into extrinsic and intrinsic factors. Among the extrinsic factors, chemicals, UV radiation, dietary imbalance are of more importance. However, the cancer initiation, promotion, metastasis, angiogenesis are major intrinsic factors. Initial step in carcinogenesis involves the metabolic activation of chemical carcinogens by the P-450-dependent biotransformation reaction responsible for the metabolism of pro-carcinogens to their DNA binding metabolites. This binding to DNA is considered essential for tumor initiation. The modulation of phase-I and phase-II enzyme system are primary target of chemopreventive agents. Activation of phase-I and phase-II enzymes is dependent upon activation of signal transduction pathways e.g. Nrf2, antioxidant-responsive element (ARE), MAPK pathway, extra-cellular signal-regulated kinase 2 (ERK2), *c-Jun*

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N-terminal kinase 1 (JNK1). In the second step, inflammatory responses play key role in cancer insurgence promoting angiogenesis.

Controlling the process of inflammation and its mediators are second target for anticancer perspectives of any drug or natural products. There are several pathways for controlling the inflammatory responses in cancerous cells i.e. oxidants, MAPK, COX, LOX, phosphatidylinositol-3 protein kinase (PI3) pathway, Nuclear factor kappa B (NF- κ B), chemokines, and G protein. The controlling the cell cycle is another potential mechanism and various studies have presented different critical points. Likewise, controlling the cellular proliferation is another possible route for chemopreventive potential of green tea and its components. This effect is particularly mediated through modulation of activities of EGFR tyrosine kinase, platelet-derived growth factor receptor, fibroblast growth factor receptor, MMP's, tyrosine kinase (PTK), *c-jun* mRNA, phosphorylated JNK1 and JNK1-kinase. The cancerous cells can be reduced through the process of apoptosis and necrosis. The chemopreventive agents that could modulate apoptosis might be effective against cancer insurgence. Therefore, chemopreventive agents with ability to induce apoptosis of cancer cells certainly have wider implications for the management of cancer.

The anticancer perspectives of green tea catechins have been highlighted in the last few decades. The studies suggested that multiple mechanisms are involved that include induction of apoptosis, cell cycle arrest down-regulation of telomerase, inhibition of

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vascular endothelial growth factor and suppression of aromatase activity (Sartippour et al., 2002; Mittal et al., 2004; Way et al., 2004; Stuart et al., 2007). Green tea catechins are flavanols possessing strong nucleophilic centers at two positions. The chemical nature of catechins strengthened them to inhibit carcinogenic species (Fesus *et al.*, 1995).

Green tea and its bioactive molecules hold the ability to inhibit cell proliferation, and may induce apoptosis. Moreover, they modulate the immune system through activation of signal transduction pathways. However, some scientific intervention, cohort studies, and meta-analysis suggested that green tea intake is not effective in all populations e.g. smokers and ex-smokers are at risk of lung cancer if they keep consuming green tea. Moreover, excessive tea consumption more than four cups in a day is also troublesome. Nevertheless, the effectiveness of green catechins in large tumors and UVB induced tumors is very limited. Under such circumstances, the green tea is ineffective in mitigating the damage caused by cancer insurgence. The synergistic and antagonistic effect of green tea catechins with other drugs/natural products needs further attention as some studies suggested that EGCG can help curcumin against cancer insurgence. The Japanese Public Health Center-based Prospective Study (JPHC) highlighted the association between green tea consumption and decreased risk of cancer insurgence (Mohan et al., 2007). The instant discussion is a message for adopting "designer approach" to get maximum benefit from green tea catechins thereby built up module for cancer prevention and cure.

III. Conclusions

The recent developments in the domain of nutrition lead to consensus that natural products especially botanicals are of significance importance in human health. Green tea has widely been acknowledged for its role in maintaining normal functionality of human beings. The health promoting properties of green tea are often attributed to its bioactive constituents especially catechins. The effectiveness of green tea catechins as chemopreventive agent has been highlighted in number of scientific interventions. Likewise they are helpful in mitigating the cancer insurgence at different phases e.g. initiation, promotion, metastasis, and angiogenesis. Mode of action is multidimensional ranging from free radical scavengers to activation/inhibition of signaling cascade. The anticancer perspectives of green tea catechins include their ability to inhibit colon, prostate, skin, lung, and breast cancer. However, some controversial inferences from cohort studies and meta-analysis are creating hindrance for their effective use as chemotherapeutic drug. Furthermore, the concept of personalized medicine, nutrigenetics, and nutrigenomics ought to be investigated for meticulousness. In the nutshell, green tea catechins hold potential to prevent malignancy and can be utilized as adjunct in cancer therapy.

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Table 1: Major Catechins in Green tea

SSr. No	Compound	Structure	IUPAC name	Mol. Formula	Mol. Weight
11	Catechins		(2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	C ₁₅ H ₁₄ O ₆	290.27 g/mol
22	Epicatechin (EC)		(2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	C ₁₅ H ₁₄ O ₆	290.27 g/mol
33	Epicatechin gallate (ECG)		[(2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate	C ₂₂ H ₁₈ O ₁₀	442.4 g/mol
44	Epigallocatechin (EGC)		[(2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate	C ₁₅ H ₁₄ O ₇	306.27 g/mol
55	Epigallocatechin gallate (EGCG)		[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)chroman-3-yl]3,4,5-trihydroxybenzoate	C ₂₂ H ₁₈ O ₁₁	458.38 g/mol