Going Green: The Role of the Green Tea Component EGCG in Chemoprevention

Laura Schramm*

Department of Biological Sciences, St. John's University, NY 11439, USA

Abstract

Tea is one of the most consumed beverages worldwide, and green tea is the least processed from the buds of the *Camellia sinensis* plant. The most abundant component of green tea is (-)-epigallocatechin-3-gallate (EGCG), which has been the focus of many cell culture, animal and clinical trials, revealing that EGCG possesses antiproliferative, antimutagenic, antioxidant, antibacterial, antiviral and chemopreventive effects. In this review we briefly summarize the mechanism of action(s) of the green tea component EGCG, highlighting recent advances in the epigenetic regulation by EGCG. Additionally, we provide an overview of mouse chemoprevention studies and EGCG chemoprevention clinical trials.

Keywords: EGCG; Green tea; Cancer; Chemoprevention

Introduction

Tea is one of the most consumed beverages worldwide, second only to water, and is produced from the buds of the *Camellia sinensis* plant. The three major tea types, green, oolong and black teas, all have various processing methods. Green tea is the least processed of the teas and contains less caffeine than both oolong and black teas [1,2]. Approximately 78% of the worldwide tea production is black tea, whereas green tea, mainly consumed in China and Japan, constitutes about 20% [1,2]. The tea plant is considered native to south China and is now cultivated in many other countries. The major tea-producing countries are China, India, Japan, Sri Lanka, Indonesia and Central African countries. The synthesis of catechins and flavonoids by *Camellia sinesis* leaves occur during the day and are temperature dependent. The major catechins, a group of polyphenols, in green tea include: (-)-Epigallocatechin-3-Gallate (EGCG); (-)-Epigallocatecin (EGC); (-)-Epicatechin (EC); and (-)-Epicatechin Gallate (ECG) (Figure 1), EGCG being the most abundant and best studied (Table 1) [2].

Many studies have demonstrated that green tea, particularly EGCG, possesses antiproliferative [3-6], antimutagenic [7,8], antioxidant [9-11], antibacterial [12], antiviral [13,14] and chemopreventive effects [15-23]. Green tea polyphenols, and its major constituent EGCG, have been tested in tissue culture [24-27], animals [3,28-33] and more recently in clinical trials [14,34-38].

In this review we briefly summarize the mechanism of action(s) of the green tea component EGCG, highlighting recent advances in the epigenetic regulation by EGCG. Additionally, we provide an overview of mouse chemoprevention studies and EGCG chemoprevention clinical trials.

Mechanisms of EGCG Action

Numerous tissue culture studies have identified multiple mechanisms for green tea, most notably for EGCG, in chemoprevention. EGCG has been demonstrated to regulate signal transduction pathways including: JAK/STAT [39]; MAPK [40,41]; PI3K/AKT [42-44]; Wnt [45,46]; Notch [47-49]; NF-κB [50-53] and AP-1[41]. Additionally, green tea has been demonstrated to induce a host of tumor suppressor activities such as: p53 [54-57]; p21 [58,59]; p16 [60] and Rb [61] known to play a role in chemoprevention [62-64]. EGCG has also been shown to play a role in regulating a variety of receptors involved

in a host of biological functions. For example, EGCG regulates the activity of the 67-KDa laminin receptor, originally identified as part of the Extracellular Matrix (ECM) functions as part of the translational machinery and as a cell surface receptor [65-69]. Moreover, EGCG can regulate activity of the Androgen Receptor (AR) in prostate cancer [70-72] and the Estrogen Receptor (ER) in breast cancer [73,74].

Epigenetic Mechanisms of EGCG

Nutrients and bioactive food components, including green tea, have been demonstrated to induce epigenetic changes, including alterations in histone modifications and DNA methylation (Figure 2) [75,76]. Hypermethylation of promoter regions, CpG islands, is an effective means to silence genes including tumor suppressors, DNA repair enzymes and other genes encoding proteins regulating cell proliferation [28,73,77-79]. Histone acetylation leads to increased gene expression and is regulated by the opposing actions of Histone Acetyltransferases (HATs) and Deacetylases (HDACs), which have been demonstrated to be influenced by dietary compounds [80].
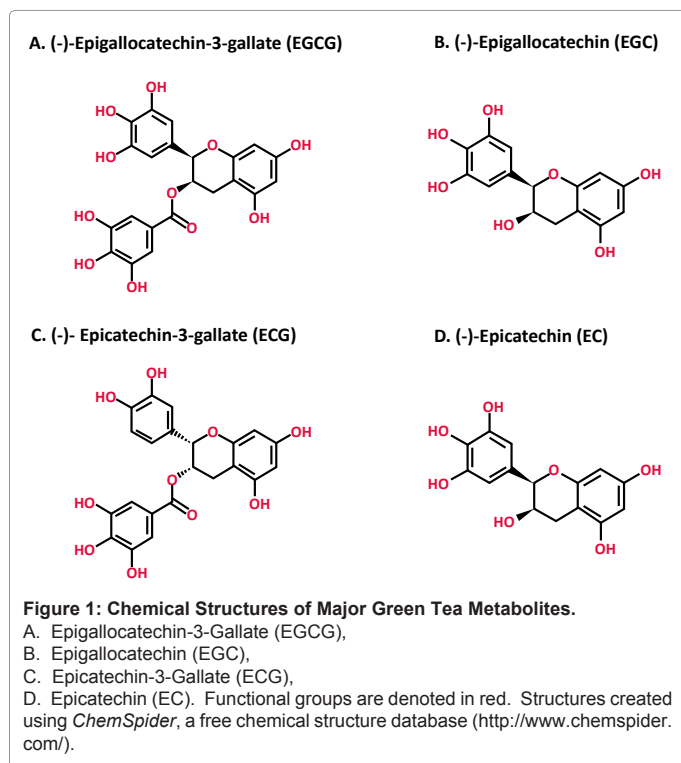
In eukaryotic cells, RNA polymerase II and III promoter activity is inhibited by promoter specific methylation [81], which occurs through the actions of DNA methyl transferases (DNMT1, DNMT3a, DNMT3b) [82]. EGCG has been demonstrated to inhibit the activity of DNMT1 [83]. The activity of RNA polymerase III has been shown to be inhibited by EGCG [84], and more recently RNA polymerase III transcription is modulated by DNMT1 and DNMT3a [85], suggesting that regulation of RNA polymerase III transcription by EGCG may occur via DNA methyltransferases. Also, the methylation of the Gluthathione-*S*-Transferase Pi (GSTP1) promoter is a molecular marker for prostate cancer and has been demonstrated in over 90% of invasive cancers of prostate origin and 70% of Prostatic Intraepithelial

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*Corresponding author: Laura Schramm, St. John's University, Department of Biological Sciences, 8000 Utopia Parkway, Queens, NY 11439, USA, Tel: 718-990-5558; E-mail: mailto:schramml@stjohns.edu

Figure 1: Chemical Structures of Major Green Tea Metabolites.
A. Epigallocatechin-3-Gallate (EGCG),
B. Epigallocatechin (EGC),
C. Epicatechin-3-Gallate (ECG),
D. Epicatechin (EC). Functional groups are denoted in red. Structures created using *ChemSpider*, a free chemical structure database (http://www.chemspider.com/).

Neoplasia (PIN) lesions [86]. The loss of GSTP1 expression correlates with decreased prostate cancer survival [87]. Green tea polyphenol treatment inhibited DNMT activity, effectively reactivating GSTP1 expression which may be beneficial in patients with prostate cancer [88]. Recent studies have demonstrated that EGCG induces epigenetic changes modulating hTERT activity, the catalytic subunit of telomerase, which is overexpressed in 90% of cancers [89,90] through inhibition of DNMT and HAT activity [91]. Furthermore, EGCG has been demonstrated to inhibit promoter methylation of the tumor suppressors' p16 and p15, thereby restoring expression in colon cancer cells [92]. EGCG also inhibits the methylation of the promoter region of the *p21/waf1* and *Bax* genes in prostate cancer cells [93]. Taken together, these data suggest that dietary compounds, such as green tea, can modulate epigenetic regulation of gene expression and have the potential to play a pivotal role in chemoprevention [94].

EGCG as a Chemopreventive in Mouse Models

"Cancer chemoprevention" was a term first introduced in 1976 by M. Sporn, who defined cancer chemoprevention as the prevention of the occurrence of cancer by the oral administration of one or multiple compounds [95]. During the compilation of this manuscript, a query of EGCG and chemoprevention in the PubMed database indicates there are 154 published studies on EGCG as a chemopreventive agent in mouse cancer models. EGCG exhibited chemopreventive activities in lung, prostate, breast, colon, oral and skin cancers in mouse models.

One study demonstrated that the differential expression of 88 genes in lung tumors compared with normal tissues was reversed by green tea treatment in A/J mice. These authors also identified 17 genes that are altered by tea treatments in both normal lungs and lung adenomas, suggesting that these genes could be used as markers for tea exposure [96]. Also, researchers have demonstrated the prevention of mammary carcinogenesis in C3H/OuJ mice by EGCG [97]. Green tea inhibits development and progression of prostate cancer in transgenic

adenocarcinoma of the mouse prostate [98-100]. Additionally, colon cancer prevention activity by tea polyphenols has been clearly demonstrated in mouse models, but results from studies in rat models have yielded inconsistent results [101]. EGCG has also been successful in inhibiting oral cavity cancer in C3H/HeJ mice [102]. Taken together, these data suggest that green tea, especially EGCG, exhibits chemopreventive properties in mouse models.

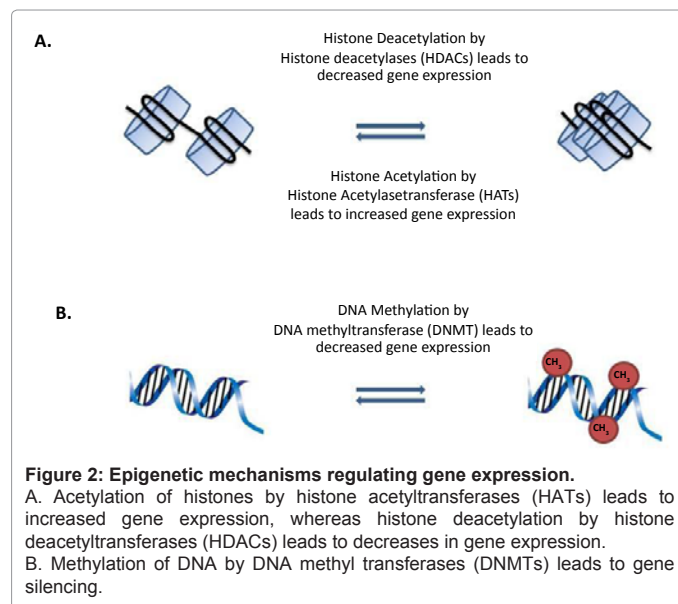## EGCG as a Chemopreventive in Clinical Trials

The 2013 cancer statistics reveal that cancer incidences have declined slightly for men, 0.6%, and remained unchanged for women during 2005-2009 [103], suggesting that more efforts are needed to develop chemoprevention therapies. In 1987, EGCG's chemopreventive effect was first reported when the inhibitory effects of EGCG on teleocidin-induced tumor promotion in mouse skin was observed [104]. There is an increasing amount of evidence that has been presented, indicating that green tea may be chemopreventive [105].

For example, clinical trials in prostate cancer patients suggest that green tea may play a role as a chemopreventive agent in progression [36]. In Japan, a study including 49,920 males aged 40-69, found that drinking greater than 5 cups of green tea per day showed a reduced risk of developing advanced prostate cancers [106]. Additionally, a double blind randomized trial of 60 patients recently diagnosed with High Grade Prostatic Intraepithelial Neoplasia (HG-PIN), who have a 30% likelihood of developing one year post HG-PIN diagnosis, was treated with green tea catechins or placebo [107]. The study showed that 30% of participants receiving the placebo developed HG-PIN after one year compared to the 3% receiving green tea catechins [107]. Two year

Green Tea Constituents	Concentration (mg/8 fl oz)*
Epigallocatechin-3-Gallate (EGCG)	25–106
Epigallocatechin (EGC)	49–113
Epicatechin-3-Gallate (ECG)	4–36
Epicatechin (EC)	6–19

* fl oz = fluid ounce, mg = milligram, L = liter [2].

Table 1: Major catechin classes identified in green tea.

Figure 2: Epigenetic mechanisms regulating gene expression.
A. Acetylation of histones by histone acetyltransferases (HATs) leads to increased gene expression, whereas histone deacetylation by histone deacetyltransferases (HDACs) leads to decreases in gene expression.
B. Methylation of DNA by DNA methyl transferases (DNMTs) leads to gene silencing.

follow up studies were performed and indicated that green tea catechin prevention was long lasting [108].

Prostate cancer is not the only cancer for which green tea catechins have been demonstrated as a chemopreventive. Recently, studies provide evidence that EGCG has potential to halt carcinogenesis in patients with Head Neck And Squamous Cell Carcinoma (HNSCC) [109]. In a phase II trial, patients with oral premalignant lesions were administered Green Tea Extract (GTE) capsules containing 13.2% of EGCG three times a day for 12 weeks had statistically significant clinical response rates in comparison to low doses of GTE [109]. Additionally, a colon cancer chemoprevention pilot study demonstrated that administration of 500 mg of GTE tablet containing 52.5 mg of EGCG three times daily for 12 months significantly ($P < 0.05$) inhibited the incidence of secondary metachronous colon adenomas [110].

There have been clinical and epidemiological studies yielding conflicting results for a variety of cancers involving green tea, including: breast [111-113]; colorectal [114,115]; esophageal [116] and lung [117] cancers. In the case of breast cancer, a very large cohort study involving the pooled analysis of two studies with 35,004 Japanese women showed no association between green tea intake and breast cancer risk [112]. These results contradict a previous study examining the association between regular green tea consumption prior to breast cancer incidence and reoccurrence and concluded green tea consumption may be preventive against recurrence of early breast cancer [111]. Colorectal cancer clinical studies have also reported conflicting results. In one study evaluating the association between green tea consumption and colorectal cancer 69,710 Chinese women aged 40 to 70 years were interviewed to ascertain green tea consumption habits and during the six year follow up a dose response protective effect of green tea was noted for women and colorectal cancer [114]. The same protective effect was not as clear cut for male green tea drinkers and colorectal cancer [115]. Mixed results have been reported for esophageal cancers. It appears that the chemopreventive effects of green tea can be counteracted by high temperatures [116]. Also, fewer well controlled clinical studies have looked at chemoprevention of lung cancer by green tea have been undertaken. However, a few well controlled studies indicate that green tea and black tea increased the risk of lung cancer [117].

It is important to note that epidemiological studies data have been used to determine the association between green tea consumption and cancer risk and selected confounding results may be accounted for by differences in lifestyle, diet and genetic variability. Many of the green tea epidemiology studies are done with Asian populations where tea drinking is associated with cigarette smoking and alcohol consumption [118]. Therefore, larger clinical studies controlling for confounders may be warranted to determine if green tea can be used as a general chemopreventive.

Importantly, there were no serious adverse effects documented in any of these green tea clinical trials. The sample sizes for controlled clinical trials are small but nonetheless significant. Even with conflicting epidemiological studies, these small and significant clinical trials further demonstrate the need for larger-scale EGCG chemoprevention studies for a subset of cancers to determine if green tea should be included in the American Recommended Daily Amounts (RDA) as part of a healthy lifestyle.

Green tea has been demonstrated to have a plethora of health benefits including; lowering blood pressure [119], increasing insulin sensitivity [119] and cardiovascular benefits [120]. In addition, EGCG, the major component of green tea, has been implicated in a host of biochemical pathways controlling cell growth and proliferation [121,122]. Animal cancer models have demonstrated that EGCG can inhibit tumorigenesis. Although there have been conflicting results for a variety of cancers such as breast [111-113]; colorectal [114,115]; esophageal [116] and lung [117] cancers there is strong evidence from clinical trials for prostate [31,107,108], oral [109] and colon cancer [110] showing promise for the use of green tea for cancer chemoprevention.

Recent 2013 cancer statistics [103] reveal that the incidence of cancer has remained relatively constant, suggesting that larger scale carefully controlled Chemopreventivetive clinical studies using natural products, such as green tea catechins, are warranted.

Acknowledgements

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