The Importance of Green Tea and its Principle Catechin EGCg in Human Health

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EGCg is a naturally occurring polyphenol which is the principle tea catechin:-(-)epigallocatechin-3-gallate, or EGCg. It is a frequently used compound both by physicians on the cutting edge of prevention and treatment, as well as by research groups who are delving into the many applications of EGCg in human health. Green tea is comprised of 10 types of catechins. Out of these, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG), and epigallocatechin gallate (EGCg) are the most important in terms of health benefits. Approximately half of the catechin content in green tea is EGCg, which explains why green tea is the subject of much research. There are inferior green tea products which contain much less EGCg. We have seen levels as low as 13%. As it turns out, EGCg exhibits an incredibly wide range of therapeutic applications. Tea from *Camellia sinensis* L. of the Theaceae family is one of the most ancient and widely consumed beverages in the world. Tea can be classified into three types: green, oolong, and black. Green tea, which is produced from non-fermented leaves and derived directly from drying fresh tea leaves, is a popular drink consumed every day by hundreds of millions of people. Eastern cultures, in particular, have long touted green tea as having medicinal efficacy for the prevention and treatment of many diseases.

As recently as 15 years ago, there were perhaps a mere handful of papers discussing this topic. ***Now there are in excess of 16,000 references on PubMed documenting the cancer preventative, anti-inflammatory, antioxidant, anti-viral, cardio protective, endothelial restorative, neuroprotective, weight loss, glycemic control benefits, and general health benefits of green tea (1 - 208*)**. Much attention has been focused specifically on its antioxidant potential, including antioxidant benefits affecting cardiovascular protection, endothelial repair and antimutagenic potential, antiviral and anticancer efficacy, and overall antiaging effects. In fact, an expanding body of preclinical as well as clinical evidence suggests that EGCg, the major catechin found in green tea, has the potential to impact a wide variety of human diseases.

Consider endothelial function: In a double blind, placebo-controlled, crossover design study, the effects of EGCg on endothelial function were examined. The study concluded that EGCg acutely improves endothelial function in humans with coronary artery disease, and may account for a portion of the beneficial effects of flavonoid-rich food on endothelial function (207). Another study demonstrated that treatment of primary bovine aortic endothelial cells, (BAEC), increased the formation of LC#-11 and autophagosomes. EGCg normalized the palmitate-induced autophagic flux. Additionally, the researchers reported that the accumulation of lipid droplets by palmitate was markedly reduced by EGCg. This effect is thought to be due to EGCg's effect on autophagosomal degradation, or through EGCg causing increased co-localization of lipid droplets and autophagolysosomes. Collectively, these findings suggest that EGCg regulates ectopic lipid accumulation through a facilitated autophagic flux and further imply that EGCg maybe a potential therapeutic reagent to prevent cardiovascular complications (208, 210). The study specifically demonstrates that the mechanism of action of EGCg is to stimulate autophagy through a CaMKKβ/AMPK-dependent mechanism and facilitates autophagic flux. Furthermore, EGCg-stimulated lysosomal degradation leads to reduced accumulation of intracellular lipid droplets in vascular endothelial cells. These EGCg effects in vascular endothelium may

contribute to protection from lipid-mediated endothelial dysfunction and cardiovascular complications.

Previously, it has been shown that a high concentration (50–100 μM) of EGCg stimulates autophagy leading to cell death in cancer cells (44, 45). Another study reported that EGCg stimulated autophagy leads to inhibition of endotoxin- induced septic shock through EGCg-induced degradation of HMGB1, a late lethal inflammatory factor (209).

Because AMPK is an energy-sensing enzyme recognizing the AMP/ATP ratio, starvation conditions activate autophagy through an AMPK-dependent mechanism (48). Thus, EGCG may be mimicking starvation or caloric restriction conditions, which are consistent with the beneficial health effects of polyphenols, including EGCG and resveratrol (49–52). EGCG also has an anti-diabetic effect that is similar to metformin, an anti-diabetic drug that activates AMPK (53). This suggests that EGCG and metformin may have a common mechanism to ameliorate metabolic and cardiovascular disorders.

There is much research to support the notion that EGCg functions as a powerful antioxidant, preventing oxidative damage in healthy cells, but also as an antiangiogenic and antitumor agent, thereby acting as a cancer preventative and as a modulator of tumor cell response to chemotherapy. Although polyphenols are well-known as potent antioxidants, just a we see with high levels of vitamin C, a pro-oxidant effect has been associated with their pro-apoptotic effect in various types of tumor cells (219). In 1971 President Richard Nixon signed **the National Cancer Act** and officially declared a national **"War on Cancer". *Now over 4 decades and billions and billions of dollars later, despite advances in some areas such as childhood leukemia we have made very little progress!***

Leading epidemiologists all agree that the best option we have now to eradicate cancer is *early diagnosis* followed by *effective curative treatment*, i.e. *Curative Prevention.* For decades researchers have been looking for better, more accurate ways to detect Cancer as early as possible

Much of the cancer chemopreventive properties of green tea are mediated by EGCg inducing apoptosis and promoting cell growth arrest by altering the expression of cell cycle regulatory proteins, activating killer caspases, and suppressing oncogenic transcription factors and pluripotency maintaining transcription factors (206). *In vitro* studies have demonstrated that EGCg blocks carcinogenesis by affecting a wide array of signal transduction pathways including JAK/STAT, MAPK, PI3K/AKT, Wnt and Notch. EGCg stimulates telomere fragmentation through inhibiting telomerase activity in malignant cells but not healthy cells. Various clinical studies have revealed that treatment by EGCg inhibits tumor incidence and multiplicity in different organ sites such as liver, stomach, skin, lung, mammary gland and colon. Hanau et al. demonstrated that this holds true for all of the most common cancers (36). In fact, EGCg has demonstrated great potential in cancer prevention as well as treatment, and the attraction for use is further enhanced because of it's safety, low cost and bioavailability.

There is extensive research going on attempting to elucidate the molecular mechanisms of cancer chemoprevention by the green tea catechin EGCg. Dr. D. James Morre's work with ENOX2, or tNOX, shed light on the mechanism involving this universal cancer marker. Because all malignant cells produce the Exon 4 minus splice variant ENOX2 protein, and because normal cells never do, this ENOX2 protein can serve both as a therapeutic target, as well as a diagnostic parameter upon which to assess the presence of cancer cells. Although there are a

multitude of studies supporting the preventive potential of EGCg against cancer, the diversified effects of EGCg may explain its broad pharmacologic activities in modulating cellular signaling pathways in cells. EGCg, in addition to other mechanisms, at human achievable dose, is known to activate cell death signals and induce apoptosis in precancerous and cancerous cells alike, resulting in the inhibition of tumor development and/or progression (210-218). Importantly, these anti-proliferative and proapoptotic effects of EGCg have been shown to be selective for cancer cells, as normal cells were not affected by its treatment (210-218)

Another novel mechanism of action for EGCG-mediated cancer cell death was demonstrated by identifying the critical role of lysosomal membrane permeabilization (LMP). First, EGCg-induced cell death in human cancer cells (both HepG2 and HeLa) was found to be caspase-independent and accompanied by evident cytosolic vacuolization, only observable when cells were treated in serum-free medium. The cytosolic vacuolization observed in EGCg-treated cells was most probably caused by lysosomal dilation. Interestingly, EGCg was able to disrupt autophagic flux at the degradation stage by impairment of lysosomal function, and EGCg-induced cell death was independent of Atg5 or autophagy. The key finding of this study is that EGCg is able to trigger LMP, as evidenced by Lyso-Tracker Red staining, cathepsin D cytosolic translocation and cytosolic acidification. Consistently, a lysosomotropic agent, chloroquine, effectively rescues the cell death via suppressing LMP-caused cytosolic acidification. Lastly, researchers found that EGCg promotes production of intracellular ROS upstream of LMP and cell death, as evidenced by increased level of ROS in cells treated with EGCg and the protective effects of antioxidant N-acetylcysteine (NAC) against EGCg-mediated LMP and cell death. This is yet another example of an anti-oxidant functioning as a pro-oxidant in cancer cells but not healthy normal cells. Taken together, data from studies such as this reveal a novel mechanism underlying EGCg-induced malignant cell death involving ROS and LMP. Therefore, understanding this lysosome-associated cell death pathway sheds new light on the anti-cancer effects of EGCg (210).

Polyphenols in general, especially in in combination with the vanilloid capsaicin, have been shown to be the most potent and effective inhibitors of tNOX, or ENOX2 (54, 55). This is a family of proteins that are cancer-specific and growth related. They are cell-surface proteins with protein disulfide-thiol interchange and hydroquinone and NADH oxidase activities designated tNOX, or ENOX2 (57,58).

In addition to the chemoprotective and cardioprotective roles of EGCg, Chang et. al demonstrated the anti-viral effects of EGCg as early as 2003 (61). Many others followed with similar findings regarding the anti-viral effects of –(-)epigallocatechin-3-gallate, (EGCg), (59,60,61,62,64,65). Additionally, Moore's team demonstrated the anti-viral effects of this combination of EGCg and vanilloid Capsaicin in 2009 (60). Green tea catechins inhibited viral infectivity by 98 % at a concentration based on EGCg content of 1,000 nM. Inhibition of virus infectivity by the green tea catechins reached an IC 50 at about 100 nM. In contrast, the catechin–vanilloid mixture inhibited virus infection almost 100 % at a concentration of 100 nM and reached an IC 50 between 0.1 and 1 nM with concentrations based on EGCg content (66).

Moore et al and Hanau et al. demonstrated both in cell culture as well as a clinical trial, that EGCg in a synergistic mixture with a high vanilloid capsaicum was most protective in a range of 100 nM to 500nM. In fact, the vanilloid capsicum green tea mixture increased efficacy by 100 fold over either compound alone. A dose dependent relationship was observed when looking at GC and EGC. While GC and EGC showed antiproliferative effects in a dose-dependent manner, after GA esterified with them to compose GCG and EGCg, their antiproliferative effects were

further increased. Overall, except for C and EC, the tea polyphenols possess different cancer protective potentials, and EGCg shows the most potent antiproliferative activities. It is no wonder that this catechin has been the focus of so much research in these past few years!

The role of green tea, in particular EGCg, and all of its various oxidation products, in human health is nothing less than staggering!

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