The Immunological Benefits of Green Tea (*Camellia sinensis*)

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Abstract

This paper explores the health benefits of green tea (*Camellia sinensis*). Green tea is known for its health benefits. Its primary impact is through the immune system. The paper begins with an overview of tea's properties according to Chinese traditional medicine, and outlines the main impacts of green tea on T-cells. By reviewing more contemporary studies using green tea extract, the health impacts are quantifiable and epidemiological studies also indicate the link to improved health outcomes in terms of chronic ailments such as diabetes. This paper examines some of the ways in which tea is currently consumed, with an emphasis on how green tea is processed in order to maximize its health benefits. Focusing on EGCG found in green tea, this paper discsses some of the dosages and their impacts, as well as some of the negative impacts of other caffeinated beverages. While further research in this area would reveal more in terms of the limitations on safe consumption associated with these benefits, and exploring the mechanisms through which they take place. This paper concludes that drinking green tea regularly is a safe and inexpensive way for most people to maintain good health.

1. Introduction

The link between green tea and immunity has been accepted for centuries in Eastern cultures, whereas Western culture has only been aware of its benefits for a few decades. Chinese medicine theory states that green tea has cooling characteristics since its taste is bitter and sweet. As recorded in the Chinese diet therapy textbook of Food and Nutrition, green tea can clear the mind, increase alertness, reduce stress, and improve mood (Vinson, 2000). There is an old saying in China that "Better to be deprived of food for three days, than tea for one," and according to Lu Yu, the author of the *Classic of Tea,* "Tea tempers the spirit, harmonizes the mind, dispels lassitude and relieves fatigue, awakens the thought and prevents drowsiness" (Yu, 1995).

Today, tea, ginger, honey, black pepper, spices, onion, and garlic are considered as important foods that help improve human immunity (Vinson, 2000). Compared with other foods, green tea shows many potential benefits to human health without the negative side effects of synthetic drugs, which makes it a promising area of research. An interesting correlation presently observed is that Asian populations that routinely consume green tea enjoy a longer life span and lower rate of disease than Western populations (Monique et al., 1996).

Tea is currently one of the most popular beverages consumed worldwide after water, because of its purported health and beauty benefits that laboratory studies have shown in the immunological function. Green tea is easy to consume in a variety of forms from traditional drinking to supplemental tablets (Lin et al., 2014). Within traditional drinking, tea is divided into five major groups based on how tea leaves are processed: green, black, white, oolong, and pu-erh. Different groups of tea affect health in different ways. Green tea leaves are plucked, partially withered and heated to 200 degrees Celsius to prevent fermentation. The dried leaves are then rolled and heated again. Green tea contains the highest concentration of Epigallocatechin-3-gallate (EGCG) compared with other teas.

2. The Role of Tea in Epidemiologic Aspect

Suzuki studies the connection between tea consumption and cancer risk among Japanese elderly people (Suzuki et al., 2009). He compared people who lived in the tea producing region called Shizuoka, where they drank seven or more cups of green tea than the average Japanese, who consumes less than one cup per day. The result showed Shizuoka's people have much lower cancer rates (30%) than the average people in Japan. Green tea (*Camellia sinensis*) is such a food medicine in that it promotes health benefits by impacting the immune system.

Epigallocatechin gallate (EGCG) is the primary source in green tea, has good effects since it has been shown experimentally to positively affect to the immune system. Epigallocatechin gallate (EGCG) is by far the most important catechin in green tea which constitutes about 50 to 80% of the total 200 to 300 mg in a brewed cup of green tea. EGCG is a biochemically active compound with known anti-inflammatory, anti-carcinogenic, and free radical-scavenging properties. In addition, there are varying numbers of studies done which holds up the argument of the preventive ability of EGCG against cancer (Singh et al., 2011).

3. Inhibition of Cancer by EGCG

In laboratory studies, there is a link between cancer and EGCG in green tea. EGCG has substantial free radical scavenging activity which leads to inhibit cancer development. Riley's studies showed free radicals play an important role in cancer cellular development (Riley, 1994). They are highly reactive chemicals that contain the element oxygen that have potential to harm cells. At high concentration, free radicals can interact with cells that cause damage to all major components of cells, including DNA, proteins, and cell membranes, that can lead to the development of cancer. According to Cadenas and Davies, antioxidants are chemicals that interact and block the activity of free radicals to prevent cell damages (Cadenas & Davies, 2000). Antioxidants come from two sources. The first source is made naturally by the body which is called endogenous antioxidant, and the second source comes from the diet which is called dietary antioxidants. Fruits, vegetables, and grains are rich sources of dietary antioxidants. In laboratory and animal studies, high amounts of exogenous antioxidants was shown to prevent the types of free radical damage that have been associated with cancer development (Serra-Majem et al., 2006; Rahman, 2003). Therefore, EGCG shows a potential in the treatment of cancer, because of its antioxidant activity. But there are no studies that showed the relationship between the effect of EGCG on the immune system through regulatory T cell and IgE, and antioxidant in cancer disease.

4. Anti-inflammatory Effect of EGCG

From the immunological standpoint, laboratory studies had suggested that EGCG is a strong, potent, and largely effective anti-inflammatory substance that can inhibit production and proliferation of several immune system molecules which cause inflammation and joint damage (Brahma et al., 2011). Based on Zhang et al's research results, he found out that EGCG inhibits imiquinod-induced prosiasis-like inflammation of BALB/c mice (Zhang et al., 2016). Psoriasis is a symptomatic disorder associated with chronic inflammation of the immune system with unestablished pathogenesis. It majorly affects the T cells and the IL-23/IL17 strain is largely believed to be critical in its pathogenesis. In Zhang et al.'s research conducted on mice which have a strain of psoriasis, the mice were topically treated with IMQ for 6 consecutive days. During the experiment, topical application of EGCG and treatment with EGCG were conducted separately and the effects of the two methods were observed on mice with psoriasis-like dermatitis. The results shows that topical application of EGCG lessened the severity of psoriasis-form dermatitis, improved the skin's pathological structure by reducing the expression of epidermal proliferating cell nuclear antigen (PCNA). PCNA, a 36 kDa nuclear non histone protein polypeptide is one of the active markers of cell proliferation (Pal et al., 2015). Treatment of psoriasis-like dermatitis with EGCG reduced the effects of skin inflammation, accompanied by little or no infiltrations of T cells; tiny percentages of CD11c(+) DC in the composition of spleen immunocytes; reduced levels of interleukin (IL)-17A, IL-17F, IL-22, IL-23 and malondialdehyde (MDA) in plasma; increased percentages of CD4(+) T cells in the composition of immunocytes of spleens; and improve bio-activities of superoxide dismutase (SOD) and catalase (CAT) in the blood plasma (Zhang et al., 2016). Analysis of the results established that EGCG had anti-inflammatory, immune regulatory and antioxidant effects. This gives a promising breakthrough in the treatment of psoriasis in the near future.

5. *In Vitro* Studies of EGCG on IgE Responses

5.1 EGCG Inhibit B Cell Production of IgE without Inducing Apoptosis

Ehab Hassanain has performed research on the immunoregulatory effects of EGCG from green tea extract on the human immune system caused by suppression of immunoglobulin E (IgE) from B cells (Hassanain et al., 2010). Immunoglobulin E (IgE) is one of five classes of antibodies in the human immune system. IgE plays an important role in type I hypersensitivity often linked to a host of allergy based diseases such as asthma, sinusitis, and food allergy (Macglashan et al., 2014). Although IgE is less abundant than other antibodies, it is capable of triggering the most potent inflammation reactions. IgE plays an important role in allergic inflammation. In immunological studies, allergy is defined as a hypersensitivity reaction mediated by antibody or cell-mediated in the immunological mechanisms (Macglashan et al., 2014). In the majority of cases the antibody responsible for an allergic reaction belongs to the IgE isotype and individuals may be referred to as suffering from an IgE-mediated allergic disease such as IgE-mediated asthma. Atopy is a personal or familial tendency to produce IgE antibodies in response to low doses of allergens. As a consequence, individuals with a family history of atopy have a major

risk factor for the development of allergic diseases such allergic asthma, rhinitis or atopic dermatitis/atopic eczema. So further study of the mechanism behind green tea's suppression of IgE could be benefit for the therapeutic efficacy in allergies, asthma, and atopic dermatitis (Wu et al., 2012)

Ehab Hassanain studied how green tea extract (GTE) can affect IgE production by B cells *in vitro* (Hassanain et al., 2010). His aim was to investigate the immunoregulatory effect of GTE on IgE production, and whether the effect of GTE on IgE was due to apoptosis of B cells or independent of cell death in model U266 cells. The U266 cell line is a B lymphocyte cell type associated with myeloma/plasmacytoma disease. U266 myeloma cells, which secrete IgE, were cultured for 72 hours with or without green tea extract. The experiment was divided into three parts: U266 myeloma cells with no GTE treatment, a single GTE treatment once per day, and multiple GTE treatments per day, and took place over three days. U266 cells were given a treatment dose of 1-300ng/ml GTE. The results showed that with no treatment, IgE levels were detected and continued increasing after 12 hr. GTE treatments showed suppression of IgE production and there was a stronger suppression of IgE production in multiple GTE treatments compared with single GTE treatment (Hassanain et al., 2010). It is important to test whether GTE suppression IgE was related to myeloma U266 cell death. Multiple myeloma is a malignant homeopathy caused by the accumulation of slow proliferation and apoptosis-resistant cells in the bone marrow. Cell counts in all three experimental groups fell within similar ranges. Therefore, the hypothesis that GTE cause apoptosis of B cells was disproven (Hassanain et al., 2010).

5.2 EGCG Inhibit IgE Production in Peripheral Blood Mononuclear Cells

Laboratory analysis of a pilot study done by Smith-Norowitz et al. demonstrated how Epigallocatechin gallate repress Chlamydia pneumonia and also brought about IgE responses in peripheral blood mononuclear cells: a pilot study (Smith-Norowitz et al., 2016). Green tea extract (GTE) can affect IgE production by B cells *in-vitro.* Chlamydia pneumoniae (C. pneumoniae) causes respiratory infection in children and adults and is associated with asthma and induction of immunoglobulin E (IgE) responses. The study clarifies the in-vitro effect of EGCG on C. pneumoniae and also mediated IgE responses by peripheral blood mononuclear cells (PBMC) in asthma. Elevated IgE levels were detected in supernatants of PBMC from an asthma patient (2.6 ng/mL), whereas IgE levels of PBMC from non-asthmatics were insignificant (<2.0 ng/mL) at baseline. When EGCG (0.5-50 ng/mL) was added to PBMC from the asthma patient, IgE production was suppressed in a dose-dependent manner (10-30%), compared with no EGCG. When PBMC from the asthma patient were incubated with C. pneumoniae, IgE production was suppressed (70%); when PBMC from non-asthmatics were incubated with C. pneumoniae, IgE levels remained undetectable (<2.0 ng/mL). When EGCG (0.5-50 ng/mL) was added to PBMC from the asthma patient, C. pneumoniae-induced IgE production was suppressed moderately (35-48%) (Smith-Norowitz et al., 2016). Clearly, EGCG suppressed C. pneumoniae- mediated IgE responses in PBMC from a patient with asthma.

Recent studies in our laboratory demonstrated the suppression of immunoglobulin E (IgE) production by green tea extract (GTE) in U266 cells (Wu et al., 2012). However, the effects of GTE or one of its components (EGCG) on IgE production by human peripheral blood mononuclear cells (PBMC) are unknown. PBMC (1.5×10^6) obtained from serum IgE+, allergic asthmatic patients, were cultured ± GTE (1-100 ng/ml) or purified EGCG (0.5-50 ng/ml), and IgE levels were determined on day 10 by enzyme-linked immunosorbent assay (ELISA). High levels of IgE were detected in supernatants of the PBMC cultures on day 10. When GTE was added to the mix in-vitro, IgE production by PBMC was suppressed on day 10, compared with control. Purified EGCG included in-vitro also suppressed IgE production, but at lower levels when compared with control. This study demonstrates that GTE and its major catechin, EGCG, have immuno-regulatory effects on human IgE responses (Wu et al., 2012).

6. Induction of Regulatory T Cells by EGCG

Green tea is not only beneficial to suppress IgE production, it also aids in the regulation of T-cell level in the immune system. Regulatory T cells (T_{reg}) are a component of the immune system that suppresses the immune responses of other cells, an important self-checking mechanism built into the immune system to prevent excessive reaction. Regulatory T cells express CD4, CD25, or Foxp3 (Kang et al., 2007). T_{reg} plays a critical role in the control of autoimmunity and maintenance of tolerance self-antigens (Wood et al., 2003). In autoimmune diseases, our immune system starts producing antibodies to our tissue or an organ, treats it as a foreign substance and starts rejecting the tissue or organ which lead to the death of our own cells. With its ability to suppress reactions of other immune cells, T_{reg} prevents the process of autoimmunity to protect cells. In the case of a transplant, when a person receives an organ from someone else, that person's immune system may detect the antigen on the cell of a newly transplanted organ as foreign cells and start to attack and destroy the organ's cells. Many studies indicate T_{reg} acts as a regulator or suppressor of immune responsiveness. Therefore, it helps to silence an immune response from

attacking the newly transplanted organ of recipient body to donor organ (Wood et al., 2003; Feuerer et al., 2009; Vignali et al., 2008). Epidemiological studies have indicated that Chinese and Japanese populations that traditionally consume large quantities of green tea have one of the lowest disease incidences of autoimmune type 1 diabetes (Gallo et al., 2013; Yang et al., 2014). These cells are involved in shutting down the immune response after they have successfully eliminated invading organisms, and in preventing autoimmunity (Tang et al., 2004).

Laboratory studies also showed EGCG in green tea can control gene expression through epigenetic modification which affects the regulation of the immune system and enhances the number of regulatory T cells (T_{reg}) (Pae & Wu, 2013; Wang et al., 2013). Foxp3 is a molecule that functions as the promoter of genes involved in regulatory T cell function, and may aid in the suppression of transcription of key genes following T cell receptor stimulation (Kang et al., 2007). Wong studied how epigallocatechin gallate (EGCG) in green tea can function as a trigger to the immune system through regulatory T cells, he examined the ability of EGCG to induce T_{reg} cells *in vitro* and *in vivo* (Wong et al., 2011).

5.1 Green Tea and EGCG Effect on Foxp3 Expression

Based on Foxp3's functions, Wong hypothesized that EGCG in green tea can induce the Foxp3 promoter that leads to the differentiation and expansion of T_{reg} cells (Wong et al., 2011). Wong's *in vitro* treatment tested his hypothesis by comparing the ability to induce Foxp3 expression in CD4 T cells between Aza and EGCG in Jurkat cells line. The results showed that both EGCG and Aza induced a significant increase in Foxp3 expression. Next, he continued to have two subtests to determine if EGCG induced Foxp3 expression in a dose-dependent fashion and whether green tea, as a whole food, could also affect inducing Foxp3 expression (Wong et al., 2011). For the first subtest, the data showed 2 μM and 10 μM EGCG concentrations have similar ranges to induce Foxp3 expression. For second subtest, Wong compared treated Jurkat T cells with diluted green tea containing the equivalent concentrations of 10 μM and 50 μM EGCG instead of comparing Jurkat T cells incubated at 10 μM and 50 μM EGCG. As a whole food, Foxp3 expression was significantly increased with green tea at 50 μM. But cells treated with green tea at 10 μM did not significantly induce Foxp3 expression. This result of two subtests were different and we cannot explain what caused the difference in the expression of Fox3p of the Jurkat T cells when exposed to only EGCG and EGCG in green tea since the mechanism of EGCG is unclear.

Wong's *in vivo* treatment was carried out with 8-week old mice that were separated into two groups, untreated mice and mice which were injected daily with 50mg/kg EGCG per mouse for seven days (Wong et al., 2011). The experiment showed that mice treated with EGCG *in vivo* had significantly increased T_{reg} numbers in the spleen, pancreatic lymph nodes, and mesenteric lymph nodes. The test showed that mice treated with EGCG had significantly reduced T cell proliferative capacity when stimulated with anti-CD3 *in vivo*. Reduced T cell proliferation strongly correlated with significantly reduced production of Interferon- γ, an important activator of macrophages and interleukin-2 (IL-2), a signal molecule necessary for proliferation and differentiation of effector T cells (Yee et al., 2013). Furthermore, stable expression of Foxp3 is crucial for maintaining the T_{reg} phenotype and suppressive function of the immune system (Campbell & Ziegler, 2007). *In vitro* study showed that EGCG affect the expression of Foxp3. Therefore, induction or expansion of T_{reg} via green tea polyphenol EGCG has potentially significant clinical applications for the treatment of autoimmune disease that could prolong graft survival (Campbell & Ziegler, 2007).

5.2 EGCG Effect on CLL by Increasing Lymphocytosis and Tregs

Regulatory T cells (Tregs) are considered to be key immuno-modulatory cells of the immune system and are increased in chronic lymphocytic leukemia (CLL). Clinical examinations have shown that epigallocatechin-gallate (EGCG) in green tea, have anti-tumor tendencies on hematologic malignancies including CLL (D'Arena et al., 2013). Rai stage 0 identifies patients with early stage CLL which currently has no effective treatment with but the symptomatic infections are usually observed and recorded. From the clinical examinations conducted, extracts from green tea were orally administered to 12 patients with stage 0 CLL and 12 healthy individuals as the control. Ten of the 12 patients and also 10 of the 12 controls fully completed the 6-month scheduled therapy. The remaining 2 patients and 2 controls stopped therapy in the space of a month because of tachycardia and epigastralgia. Eight out of the 10 patients evaluated (80 percent) showed a reduction of lymphocytosis and total number of circulating Tregs, as well. One patient (10 percent) had a stabilization of lymphocytosis and a reduction of Tregs, and one patient (10 percent) showed an increase of both lymphocytosis and Tregs. Only the non-responding patient progressed after 5 months from the end of green tea administration and chemotherapy was given. Interestingly, both IL-10 and TGF-beta serum levels declined throughout the green tea intake period, in both patients and controls. These data seem to indicate that green tea is able to modulate circulating Tregs in CLL

patients with early stage of the disease. This can result in the control of lymphocytosis as well as in the prevention of disease progression (D'Arena et al., 2013).

7. Immunomodulatory Effects of EGCG

The characteristic behavior of one of the more significant catechins in Green Tea, EGCG have been proven to have quite a number of health benefits. Recent studies suggest that EGCG can vary the strength of both the innate and adaptive defensive abilities of the immune system (Min et al., 2015). Min et al.'s studies were to test for the immuno-modulatory effects and mechanisms of action of EGCG on arthritis in experimental mice (Min et al., 2015). EGCG (10 mg/kg) was administered on the experimental mice by oral gavage after CIA induction, while control mice were administered phosphate buffered saline (PBS). Etiology of diseases was studied in both groups of mice. EGCG treatment improved the various clinical symptoms and also reduced tissue death in arthritic mice. Serum type-II collagen-specific immunoglobulin (Ig) IgG2a antibodies significantly reduced in EGCG-fed mice compared to PBS-treated mice. EGCG significantly suppressed T cell proliferation was significantly suppressed with EGCG treatment. Also relative frequencies of CD4 T cells, CD8 T cells and B cell subsets including marginal zone B cells, T1 and T2 transitional B cells were also suppressed, while the frequency of CD4(+) Foxp3(+) regulatory T cells (Tregs) and indoleamine-2,3-dioxygenase (IDO) expression by CD11b(+) dendritic cells (DC) got increased. Splenic CD11b(+) DC from EGCG fed mice induced an increase in the frequency of Tregs presence via an IDO-dependent mechanism in in-vitro cultures. Most notably, joint homogenates from EGCG-fed mice exhibited significantly increased levels of Nuclear Factor, Erythroid 2-Like 2 (Nrf-2) and Heme oxygenase-1 (HO-1) compared with PBS-fed mice. This is the first report of upregulation of the Nrf-2 antioxidant pathway in EGCG-mediated immuno-regulation. EGCG ameliorated experimental arthritis in mice by eliciting IDO-producing DCs, increasing frequencies of T regs and inducing the activation of the Nrf-2 antioxidant pathway. It remains to be seen whether EGCG is useful for the prevention and treatment of rheumatoid arthritis and other inflammatory disorders (Min et al., 2015).

8. Tea's Health Benefits

While all teas contain high levels of antioxidant polyphenols, it is the fermentation process that makes difference between green and black teas. Although green tea is believed to have a stronger and more broad range of health benefits than black tea, recent studies have shown that both possess many health benefits. Black tea has the highest caffeine content, and may be of benefit to human health by protecting lungs from damage by cigarette smoking (Banerjee et al., 2007). It is also known to reduce the possibility of stroke (Li et al., 2012). White tea is made with uncured and unfermented tea leaves. According to Mao, Nie and Tsu's *in vitro* studies, white tea has the most anticancer properties and it is capable in inducing apoptosis in lung cancer cell lines (Jenny et al., 2010).

9. Tea Consumption and Side Effects

Drinking green tea is a safe way to consume EGCG. Though an individual can consume several cups of green tea, only 270mg of ECGC can be digested, therefore an accumulation of ECGC cannot occur. In animal studies, Oolong tea has been found to lower low-density lipoprotein (LDL) which is known as bad cholesterol (Naghma & Hasan, 2007). Too much LDL in circulating blood can cause a clot and block a narrowed artery hence leading to heart attack. Pu-erh tea helps decrease weight gain and reduces LDL cholesterol (Lanjun et al., 2011). All these teas also contain caffeine and theanine, which affects the brain and seems to heighten mental alertness (Robert et al., 2012). According to Takabayashi's studies, data showed that a high dose of EGCG in green tea had an effect on oxidative DNA damage in the pancreas and liver of hamsters (Takabayashi et al., 2004). This brings about concerns about using green tea supplemenst instead of drinking the green tea. During the day, many people consume other caffeinated beverages, such as coffee and colas, so the total caffeine they consume will be higher and could cause adverse effects such as nervousness, tremors, headache, abdominal pain, nausea, vomiting, and diarrhea (Lin et al., 2014). Besides avoiding green tea overdosing, there is a concern about green tea's effect on iron-deficiency anemia patients- who do not have enough iron to produce healthy red blood cells. According to Mira, who studies the interactions of flavonoids with iron and copper ions, black and green tea may inhibit iron bioavailability from the diet (Mira et al., 2002).

Ehab Hassanain's study showed that green tea extract suppressed human IgE production *in vitro* in a dose-dependent fashion from a mechanism other than cytotoxicity (Hassanain et al., 2010). However, suppression of IgE could be good in certain cases, but there are two major concerns. First, we do not know the right dosage that will work in humans. *In vitro* and *in vivo,* a dose of 300ng/ml concentration of GTE was used to show effect. Humans need higher doses since we are much bigger and doses must be ingested. According to Yang's study, consuming of 3.0 g green tea solid with 500ml water would get 326ng/ml of EGCG in the plasma (Yang et al., 1998). However, if more than 3g are consumed, the concentration of EGCG in plasma is still 326ng/ml. Yang

suggested the reason was due to saturation phenomenon. So we need to know the right way and concentrations to consume tea that can bring health benefit. A second concern about green tea is the polyphenol it contains has low bioavailability in serum. When humans ingest green tea, its bioactive components could have a different affect compared with the results from laboratory experiment because of the metabolism and protein binding. Furthermore, the mechanism of GTE suppression of IgE production is unknown (Yang et al., 1998).

10. Conclusion

Drinking green tea regularly is a safe and inexpensive way for most people to maintain and stimulate health. But green tea supplements need to establish a safe range for beneficial effects and prevention of harmful affect from excessive dose. Most scientific studies have substantial evidence from *in vitro* and animal studies but limited evidence in human clinical trials. Future research should define the real limits of green tea and its health benefits, establish a safe range of tea supplement consumption associated with these benefits, and elucidate the mechanisms of action.

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