

Review

Green Tea as an Agricultural Based Health Promoting Food: The Past Five to Ten Years

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Received: 5 September 2012; in revised form: 16 November 2012 / Accepted: 20 November 2012 / Published: 5 December 2012

Abstract: The consumption of tea originated in ancient China over 4000 years ago and is currently the second most popular beverage in the world after water. Tea is an aromatic beverage prepared by pouring hot water over cured leaves of the *Camellia sinensis* plant. The link between tea intake, most notably green tea, and health has resulted in intense research on the components responsible for preventing the onset of several chronic diseases, including atherosclerosis, cancer, obesity and diabetes. In particular, the high levels of chemically diverse phenols (e.g., phenolic acids, flavonoids) present in tea exhibit potent protective properties against many of these diseases. Although health related research on green tea and its predominant phenol (catechins) has been on-going for decades, major advances have occurred in the last 5–10 years. Therefore, this review focuses on seminal studies reported primarily within the last five years but not extending past ten years on the link between health and green tea with an emphasis on the catechins.

Keywords: green tea; phenols; flavonoids; oxidative stress; inflammation; health; catechins

1. Introduction

Tea originated in China over 4000 years ago and has since been a popular luxury commodity by the Asian population valued for its taste, aroma, medicinal applications, and cultural history [1]. The golden age of tea occurred during the Tang Dynasty (A.D. 618–906) as cultivation and trading routes expanded outside of China. The tea rules and ceremony developed by Lu Yu (733–804) as described in

Cha Chang or *The Classic of Tea* led to the earliest treatise on tea. Steaming of the leaves became the normal custom along with specific guidelines for processing the leaves and brewing the beverage. Lu Yu's work transformed the process into an art form and set the standard for tea cultivation/production in China. This ceremony eventually became the model that would emerge in Japan [2,3]. Tea arrived in Japan and Korea during the 6th century resulting in another highly sustainable market. Tea was subsequently introduced to Indonesia and India and then followed the trade routes into Europe (~1610), most notably Holland and England. At this point in world history, tea was considered such a high valued commodity that it was used for currency and international trade [2,3]. Tea is now cultivated in more than sixty countries with Asia (China, India, Japan, Sri Lanka, and Taiwan) producing more than 91% of the total amount annually (Table 1) [4]. While fermentation has aided in the ease of exporting tea and is a principal factor for the West's preference for black tea, green tea, or unfermented tea, is preferred in the East. However, tea drinking in North America and the Middle East of any kind is still comparatively low relative to China, Japan, and other European countries.

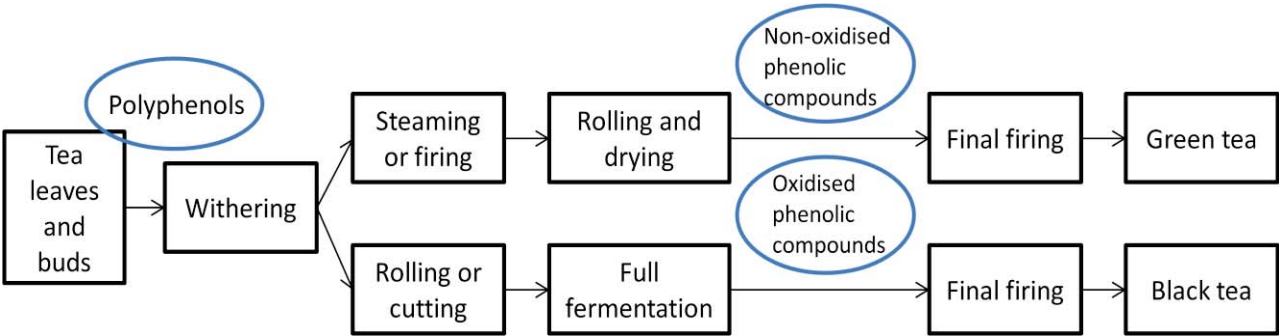
Table 1. Average annual tea production quantities by country (2005 to 2010).

Country	Quantities (tons)
China	1,217,039
India	963,313
Kenya	344,596
Sri Lanka	304,036
Turkey	209,535
Viet Nam	167,531
Indonesia	154,328
Iran	108,751
Japan	92,233
Argentina	76,071
Thailand	59,203
Bangladesh	58,763
Malawi	46,155
Uganda	41,543
United Republic of Tanzania	31,850

Data from FAO database (<http://faostat3.fao.org/home/index.html> [5]).

Green tea (GT) is made from the leaf of *Camellia sinensis* and is typically cultivated in hot humid climates [4]. Harvesting of high quality GT can simply be described as “two leaves and a bud” plucked from every new shoot. The process of GT production (Figure 1) preserves many compounds that have been linked to multiple human health properties making GT stand out from fermented black and semi-fermented oolong tea. As such, GT and its extracts have been used to enrich energy drinks, juices, vitamins, and other food systems. Of the health benefiting agents present in GT, the catechins have received major research focus [6,7]. Therefore, instead of attempting to summarize the wealth of literature published in this area, seminal studies reported primarily from the last five years but not extending past ten years will be reviewed with an emphasis on the GT catechins.

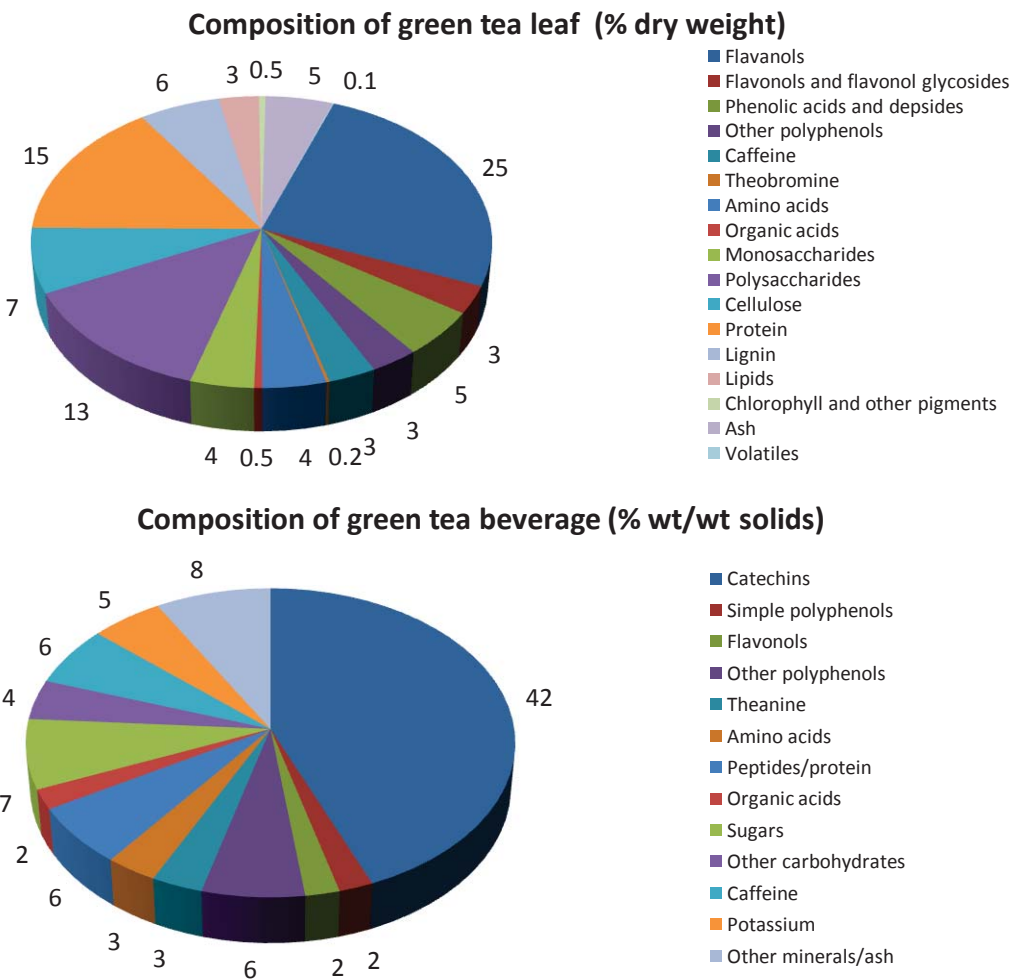
Figure 1. Tea production and its influence on the final polyphenols content (adapted from Cabrera *et al.* [8]).



2. Composition of Green Tea

Green tea is a rich source of health promoting components (nutraceuticals or bioactives) largely due to its high levels of chemically diverse phenolic compounds, which account for ~30% and 50% of the GT leaf and beverage on a dry weight basis, respectively (Figure 2).

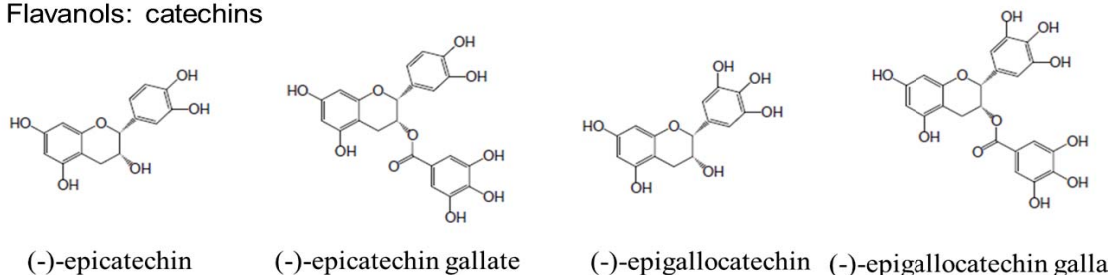
Figure 2. Principal components of green tea leaf and green tea beverages (adapted from Balentine *et al.* [9]).



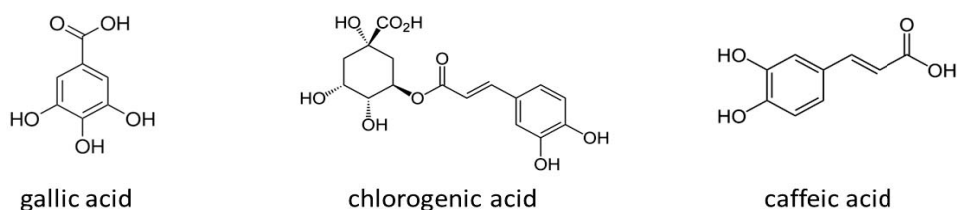
Flavan-3-ols are the major class of GT flavonoids with the catechins being the predominant form [9], including (–)-epicatechin (EC), (–)-epicatechin gallate (ECG), (–)-epigallocatechin (EGC) and (–)-epigallocatechin gallate (EGCG) (Figure 3). Among these compounds, EGCG represents ~59% of the total catechins [8]. Green tea also contains the phenolic acids, gallic acid, chlorogenic acid and caffeic acid, and the flavonols, kaempferol, myricetin, quercetin and their conjugates (Figure 2). Other flavonoids that account for a very small fraction of the tea have more recently been identified and include 19 O-glycosylated flavonols, 7 C-glycosylated flavones, 28 acylated glycosylated flavonols and 3 flavonols [10]. While not the focus of this review, it must be noted that the fat soluble compounds present in GT, such as vitamin E and the carotenoids (2% dry weight) may work with the phenols to enhance health benefits [8] albeit limited studies have been reported on possible synergistic effects. Additionally, GT contains linoleic and linolenic acids (7% dry weight) [9], which are only detected at trace levels after infusion as these compounds are involved in synthesizing the essential oils that contribute to the “green odor” [11]. Monosaccharide and water-soluble polysaccharides comprise nearly 20% of the GT leaf and are also compounds of interest due to their links to health [9]. Lastly, polysaccharide conjugates have been isolated but their structures vary depending on the origin of the tea [12,13].

Figure 3. Structure of major green tea flavonoids.

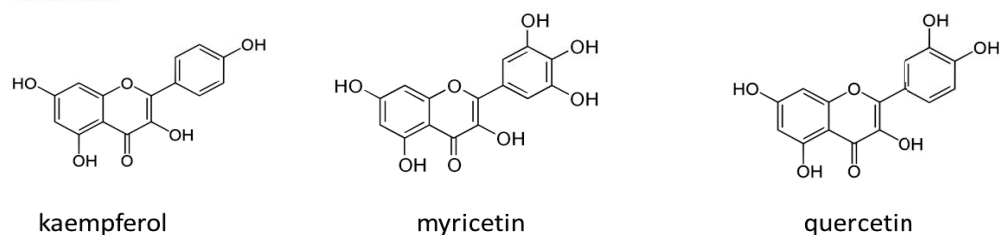
Flavanols: catechins



Phenolic acids:



Flavonols:



3. Oxidative Stress

Reactive oxygen species (ROS), such as the hydroxyl radical (OH), superoxide (O_2^-) and hydrogen peroxide (H_2O_2), maintain cellular homeostasis by acting as cell signaling agents or by regulating gene expression [14,15]. If left unchecked however ROS imbalances can cause cellular oxidative stress that can lead to chronic conditions and diseases, e.g., cancer, cardiovascular diseases and neurodegenerative diseases. Reports have shown that GT and its predominant phenols (in isolation) prevent or remediate oxidative stress via multiple mechanisms. A recent study by Schroeder *et al.* [16] showed that the most abundant GT catechin (EGCG) protected the neuron by lowering levels of mitochondrial free radicals and preventing apoptosis induced by oxidative stress. Guo *et al.* [17] demonstrated that GT catechins fed to a 6-OHDA rat model presented with reduced levels of inducible nitric oxide (NO) synthase and protein-bound 3-nitro-tyrosine. GT catechins also prevented ROS and NO generation, lipid peroxidation and increased nitrite/nitrate ratio in a dose dependent manner. GT polyphenols also play a role in reducing cellular levels of ROS generating redox-active metals. Quesada *et al.* [18] determined that EGCG binds to zinc cations with high affinity thereby reducing the accumulation of zinc in a human liver hepatocellular carcinoma (HepG2) cell model. Another study reported by Wei and Meng [19] showed that EGCG reversed lead-induced oxidative damage in ventricular myocytes isolated from rat hearts and reduced OH, O_2^- , and H_2O_2 levels.

By acting as a pro-oxidant, GT has often been linked to the apoptotic induction of tumor cells [20]. Oxidative stress induced by GT polyphenols may also trigger endogenous antioxidant systems in normal tissues. Maeta *et al.* [21] showed that 0.1% GT extract or 0.05% (1.1 mM) EGCG produced H_2O_2 in yeast models grown in weak alkaline medium. Nuclear localization of oxidative-stress-responsive transcription factors (Yap1 and Msn2 in *S. cerevisiae*, and Pap1 in *S. pombe*) were subsequently activated. Elbling *et al.* [22] reported the autooxidation of EGCG resulted in low-doses of H_2O_2 , reduced DNA damage and cytotoxicity in keratinocyte-derived HaCat cell. Additionally, these low levels of H_2O_2 initiated the up-regulation of antioxidant enzymes and lowered ROS levels. The antioxidant and pro-oxidant effects of GT polyphenols may be linked to other health benefits discussed in subsequent sections. A summary of this information and associated references are provided in Table 2.

4. Inflammation

Inflammation is the body's way of dealing with localized tissue damage/infection and is thus critical to our survival. Yet, low grade but continued stimulation of the inflammatory response can lead to chronic inflammation, which can then progress to coronary heart diseases, Alzheimer's disease, type 2 diabetes, muscle degeneration, and cancer [23–25]. Many reports have shown the anti-inflammatory properties of GT but the mechanisms eliciting the response vary between the studies.

Neutrophils are triggered at a specific site in the body by infections, tissue necrosis, necrotic cells, foreign bodies-dirt, and immune signals, including those of chronic inflammation thereby contributing to the inflammatory cycle. Dona *et al.* [26] reported that EGCG not only inhibited neutrophil elastase in an *in vitro* model but also down-modulated ROS activity, caspase-3 activity, DNA fragmentation, and the ability of neutrophils to migrate towards a chemotactic stimulus. The *in vivo* part of this study showed that EGCG inhibited neutrophil recruitment, inflammation-driven angiogenesis, and

pulmonary fibrosis. Yet another *in vivo* study completed by Shen *et al.* [27] demonstrated that fibrosis in female rats caused by chronic inflammation was significantly reduced when treated with GT catechins.

Table 2. Recent studies on green tea and oxidative stress.

References	Model	Treatment	Dosage	Main outcomes
Schroeder <i>et al.</i> [16]	Rat cerebellar granule neurons cultures	EGCG	5, 10, or 20 μ M	90%–95% of ^3H -EGCG accumulated in mitochondria. EGCG treatments resulted in reduced levels of free radicals and protected neuron from apoptosis induced by oxidative stress.
Guo <i>et al.</i> [17]	6-hydroxydopamine (6-OHDA)-treated rat model of Parkinson's Disease	GTP (98% purity) containing 50% EGCG, 22% ECG, 18% EGC and 10% EC	150, 450 mg/kg/day-fed	GTP treatment dose-dependently decreased ROS and NO level, lipid peroxidation, nitrite/nitrate ratio, and expression of inducible nitric oxide synthase and protein-bound 3-nitro-tyrosine.
Quesada <i>et al.</i> [18]	Human HepG2 cells	EGCG	10 μ M	EGCG binded to zinc cations with high affinity and thus reduced the accumulation of zinc.
Wei & Meng [19]	Myocytes from the hearts of adult rats	EGCG	0–60 μ g/mL	Formation of OH^- , O_2^- , and H_2O_2 was decreased significantly as EGCG concentration increased compared to lead treated group.
Maeta <i>et al.</i> [21]	Budding yeast <i>S. cerevisiae</i> and fission yeast <i>S. pombe</i>	EGCG and GTE	0.05% EGCG 0.1% GTE	H_2O_2 produced by EGCG and GTE induced the expression of nuclear localization of oxidative-stress-responsive transcription factors (Yap1 and Msn2 in <i>S. cerevisiae</i> , and Pap1 in <i>S. pombe</i>).
Elbling <i>et al.</i> [22]	Human keratinocytes	EGCG	0–100 μ M	Low-dose H_2O_2 and EGCG treatment enhanced the clearance of ROS and reduced DNA damage and cytotoxicity in keratinocyte-derived HaCat cell.

EGCG: (–)-epigallocatechin gallate; ECG: (–)-epicatechin gallate; EGC: (–)-epigallocatechin; EC: (–)-epicatechin; GTP: green tea polyphenols; ROS: reactive oxygen species; NO: nitric oxide; GTE: green tea extract; HaCAT: human keratinocyte line.

Regulatory T cells (T-reg) are essential in maintaining immune functions by targeting sites of sustained inflammation [28]. Recent *in vitro* and *in vivo* studies showed that EGCG (2–50 μ M) induced T-reg via the up-regulation of Foxp3, *i.e.*, a transcription factor regulated by DNA methylation [29]. The effect of EGCG on Foxp3 gene expression was similar to that of DNA methyltransferase inhibitors. EGCG also inhibited nuclear factor-kappa B (NF- κ B)-mediated inflammatory responses in mice models via the Nrf2 antioxidant signaling pathway by increasing systemic T-reg cell activity [30]. Wu *et al.* [31] investigated the ability of EGCG to suppress proliferation of T-reg in the spleen of C57BL mice. The results indicated that 2.5 to 10 μ M EGCG inhibited T-reg proliferation but did not induce apoptosis or increase oxidative stress. These researchers identified that the EGCG modulated pathway was related to IL-2/IL-2 receptor signaling.

Other mechanisms involving the inhibition of immune related cell signaling in response to GT-polyphenols have been reported. Ranjith-Kumar *et al.* [32] showed that GT-EGCG can bind to the retinoic acid inducible gene I (RIG-I) and thus interfere with interferon signaling response in mammalian HEK293T cells. Moreover, this polyphenol was able to suppress ATPase activity of recombinant RIG-I without competing with RIG-I and RNA or ATP. Analysis of the structure-activity relationship of commercially available analogs revealed that RIG-I inhibitors included epimers galocatechin gallate and theaflavin 3,3' digallate. EGCG was also shown to down regulate gene expression related to macrophage migration. Using human keratinocytes, Noh and Park [33] reported down regulation of the dexamethasone-induced macrophage migration inhibitory factor (MIF) in the presence of EGCG and the expression of MIF-induced cytokines and chemokines, such as interleukin (IL)-6, IL-18, transforming growth factor- β , CCL17, CCL22 and CXCL10, were subsequently inhibited. Ripley *et al.* [34] reported that EGCG up-regulated STAT5 transcription factor and induced the suppressor of cytokine signaling 1 gene through the superoxide pathway. These studies are itemized in Table 3.

5. Cardiovascular Health

Studies have also increased on GT intake and the promotion of cardiovascular health [35,36]. Qin *et al.* [37] showed that GT polyphenols can alter the mRNA expression of the cardiac insulin signaling pathway, regulate cardiac mRNA expression of cardiac lipid metabolism, and regulate the inflammation-related gene expression in insulin resistant rats fed a high-fructose diet. These results indicate the potential ability of GT to reduce the risk of coronary artery disease. Another study by Lorenz *et al.* [38] compared stimulus NO production and vasodilation in response to GT and black tea exposure. In the presence of the GT catechins, eNOS activity and vasorelaxation were induced by activating and phosphorylating the signaling kinases in endothelial cells. Similar results were obtained with black tea indicating that the theaflavins and thearubigins may be the responsible components. El Bedoui *et al.* [39] also showed that EGCG inhibited matrix metalloproteinase-2 activity and thus prevented vascular smooth muscle cell invasion.

Table 3. Recent studies on green tea and inflammation.

References	Model	Treatment	Dosage	Main Outcomes
Dona <i>et al.</i> [26]	Neutrophils and C57 black mice	EG CG	1–100 µM	EGCG down-modulated ROS activity, and inhibited apoptosis and chemotaxis <i>in vitro</i> model. EGCG also inhibited neutrophil recruitment, angiogenesis and pulmonary fibrosis.
Shen <i>et al.</i> [27]	3-month-old female rats	GTP (98.5% purity)	0.5% in water	The development of fibrosis in vessels and myocardium in rat decreased significantly with supplementation via down-regulation of TNF-α mRNA expression.
Wong <i>et al.</i> [29]	Human Jurkat leukemic CD ⁴⁺ T cell line and eight-week old Balb/c male mice	EGCG GT beverage	2, 10, 50 µM 2%, w/v	EGCG induced expression of Foxp3 and increased T-reg frequencies and numbers both <i>in vitro</i> and <i>in vivo</i> .
Tsai <i>et al.</i> [30]	1 2-weeks-old female NZB/W F1 mice	EGCG	120 mg/kg body weight	T-reg activity increased in EGCG treated mice.
Wu <i>et al.</i> [31]	C57BL mice spleen cells	EGCG	2.5–10 µM	EGCG targeted the pathway which is related to IL-2/IL-2 receptor signaling and inhibited T cell proliferation.
Ranjith-Kumar <i>et al.</i> [32]	Human HEK293T cells	EGCG	0–10 µM	EGCG inhibited RIG-I by binding to RIG-I and suppressing ATPase activity of recombinant RIG-I.
Noh and Park [33]	Human keratinocytes	EGCG	100 µmol/L	EGCG down regulated MIF mRNA expression and MIF induced cytokines and chemokines.
Ripley <i>et al.</i> [34]	Monocytes of human PBMCs and SOC1-deficient C57BL/6 mice	GTE and EGCG	0–200 µM	EGCG inhibited cytokine signaling 1 gene expression via inducing the SOC1 expression and un-regulating STAT5 transcription factor.

EGCG: (–)-epigallocatechin gallate; GTP: green tea polyphenols; TNF-α: tumor necrosis factor alpha; GT: green tea; IL-2: interleukin 2; RIG-I: retinoid-inducible gene 1; MIF: migration inhibitory factor; PBMCs: peripheral blood mononuclear cells, GTE: green tea extract.

Other studies have shown that GT polyphenols may function by modulating cholesterol metabolism. Bursill and Roach [40] reported decreased cholesterol synthesis in HepG2 cells when incubated with 50 μ M of GT-EGCG. However, cholesterol synthesis increased significantly using 200 μ M of GT-EGCG while cellular cholesterol remained at a low level. In the latter case, 30% more cholesterol was detected in medium indicating that higher EGCG concentrations promoted the efflux of cholesterol. Although the researchers used other GT catechins, GCG was the only catechin capable of up regulating low-density lipoprotein (LDL) receptor activity [40]. Up-regulation of LDL receptor also occurred in GT-polyphenolic fed cholesterol-fed rabbits [41]. Six experimental rabbits fed a 0.25% (w/w) cholesterol diet for two weeks followed by catechin enriched diets supplemented of 0, 0.5, 1 or 2% (w/w) for four weeks showed up-regulation of LDL receptor activity and a 60% reduction in plasma cholesterol (80% in LDL cholesterol).

Multiple human clinical studies have been completed to determine the anti-arthrosclerosis benefits of GT consumption. In one study [42], 14 healthy individuals at an average age of 30 years were separated into three groups. Each group consumed one of 450 ml of 6 g GT (brewed Lipton tea), 250 mg caffeine (amount contained in GT) or water. Flow-mediated dilatation (FMD) of the brachial artery was then measured at 30, 90, 120 min intervals. FMD significantly increased in the GT group but were similar in both the caffeine and water control groups suggesting possible benefits of GT on coronary endothelial function. Zheng *et al.* [43] identified and quantified the possible effects of a GT beverage *versus* a GT extract on human cholesterol profiles by performing a meta-analysis of 14 randomized trials reported in the literature. The researchers concluded that GT consumption had no significant effect on high density lipoprotein cholesterol in fasting serum but significantly reduced total cholesterol levels by 7.20 mg/dL and significantly decreased the LDL-cholesterol concentration by 2.19 mg/dL. In reviews by Deka and Vita [35] and Del Rio *et al.* [36], other epidemiological data providing evidence for and against GT and cardiovascular health connection are summarized.

6. Obesity and Diabetes

Metabolic syndrome is a multifaceted condition characterized by elevated waist circumference, dysglycemia, elevated blood pressure, decreased serum high-density lipoprotein-associated cholesterol, and increased serum triglycerides, *i.e.*, risk factors for diabetes and cardiovascular disease. As metabolic cases are increasing at an unprecedented rate in the US and throughout other western countries, there is considerable interest in the potential benefit of tea consumption for prevention of metabolic syndrome [44]. Numerous *in vitro* studies and animal models have shown beneficial effects of GT catechins on several of these risk factors, including reduced body fat, improved glucose tolerance and maintenance of a healthy cardiovascular system. As studies specific to GT and cardiovascular health have been discussed in the previous section, select obesity and diabetes related research will be presented in this section.

Several studies using animal models investigated the possible relationships between GT phenols and the development of obesity and other related disease risk factors. Bose *et al.* [45] reported that three month old obese mice fed a high fat (HF) diet but supplemented with EGCG not only attenuated the development of metabolic syndrome but also reversed the symptoms. Body weight, body fat, blood glucose, plasma insulin, plasma cholesterol, inflammatory markers and liver fat were all significantly

lower in 16 weeks for the mice fed the HF diet + EGCG compared to the control. After receiving a 3.2 g/kg EGCG supplemented diet, the visceral fat weight in the mice decreased 36% in nine weeks and blood glucose level decreased 22% in four weeks [45]. Sae-tan [46] showed that C57bl/6J mice fed a HF diet that included EGCG (0.32% dietary) for 16 weeks resulted in increased gene expression (1.4- to 1.9-fold) of several proteins involved in mitochondrial fatty acid oxidation, including nuclear respiratory factor 1, medium chain acyl coA decarboxylase, uncoupling protein 3, and peroxisome proliferator responsive element α . In addition, increased lipids in the fecal material of the mice were reported. Another proposed mechanism included modulation of fat lost via an EGCG link. Lee *et al.* [47] tested the hypothesis that EGCG promotes triacylglycerol hydrolysis by increasing gene expression of hormone sensitive lipase. In this study, lipid accumulation in 3T3-L1 adipocytes decreased significantly after a 24 h treatment with 10 μ M EGCG while cell viability was retained. Richard *et al.* [48], used male-deficient (ob/ob) mice and their lean counterparts (mice C57BL/6J mice) to investigate whether regular decaffeinated green tea intake affected body weight and lipid profiles. GT consumption resulted in significantly lower weight gain in the obese mice and associated cholesterolemia, triglyceridemia, and adiponectin concentrations but did not adversely affect the lean model.

Cao *et al.* [49] determined the possible molecular mechanistic connection between GT catechins using a high-fructose fed mice model. This study showed that 1–2 g of GT extracts influenced gene expression of several important regulators of glucose intake and insulin signal pathways. In a similar study, Hininger-Favier *et al.* [50] demonstrated the effects of GT extracts on insulin sensitivity using Wistar rats fed a high-fructose diet (FD) without or with 1 or 2 g of GT supplements for six weeks. The FD fed rats developed insulin resistance while rats fed GT supplements did not. Additionally, the rats fed the GT supplement presented with decreased levels of plasma lipid peroxidation, sulfhydryl group oxidation, and DNA oxidative damage. A recent study by Ma *et al.* [51] revealed tyrosine phosphatase (purified from *E. coli*) was inhibited in response to a GT extract. As a down regulator of both the insulin and leptin signaling pathways, inhibitors of tyrosine phosphatase are considered promising approaches to treat diabetes and obesity.

Other studies using human subjects of Asian descent have shown the benefits of GT intake in terms of reducing risk factors for obesity and diabetes [52–54]. In particular, the Ohsaki study [54], which followed 40,530 Japanese adults (aged from 40 to 79) for 11 years, revealed a strong inverse association between GT consumption and cardiovascular disease mortality. Recently, researchers at the Oklahoma State University compared body weight, lipids and lipid peroxidation in 35 obese subjects provided either a product with or without a GT extractable [55]. These results supported the Ohsaki study again positively correlating GT intake with decreased body weight, body mass index and biomarkers for lipid peroxidation (malondialdehyde and hydroxynonenals).

7. Cancer

According to Khan and Mukhtar [56], 765 reports have been published showing the potential of GT polyphenols as cancer chemoprevention agents. Therefore, only a sample of those studies is provided in this section (also refer to Table 4). For example, Ohga *et al.* [57] studied GT-EGCG as a therapeutic treatment against several different cancer cell lines. While EGCG had no adverse effect on

normal endothelial cells, it did exert anti-angiogenic properties by selectively suppressing the migration of tumor-associated endothelial cells and endothelial progenitor cells. Kato *et al.* [58] studied the response of the RECK gene, a novel tumor suppressor gene, in oral squamous cell carcinoma cell lines (oral cancer cell) treated with EGCG. The hypermethylation status of the RECK gene was partially reversed by EGCG whereas the gene expression level of RECK mRNA was significantly enhanced.

A recent *in vitro* study showed that GT-EGCG inhibited the growth of advanced prostate cancer by competitively binding to the androgen receptor (AR) and interrupting the gene expression regulated by AR [59]. EGCG acted at multiple levels including inhibiting interdomain N-C termini interaction, repressing the prostate cancer related mutant T877A and eventually inhibiting cancer cell growth. Lee *et al.* [60] obtained similar results using a prostate cancer cell line in response to GT catechins. The researchers proposed that catechins modulated AR acetylation was modulated in the presence of GT catechins thereby inhibiting the translocation of the AR protein to the nucleus. The activity was comparable to that exhibited by anti-histone acetyltransferase.

Although the cited studies were conducted with experimental cell models, many others have included tissues collected from human clinic trials (animal and human). By using six tumor related genes in 106 gastric cancer patients, Yuasa *et al.* [61] showed that methylation of homeobox transcription factor and bone morphogenetic protein 2 were inversely correlated with GT intake. Thangapazham *et al.* [62] used both a cell system and an animal model to study the inhibitory effect of GT polyphenols, with an emphasis on EGCG, on human breast cancer cells. The phenol treatments resulted in down regulating cancer related genes and inhibiting cancer cell proliferation. Moreover, GT polyphenols and EGCG induced apoptosis in cancer cells of an athymic nude mice model. In another animal study, Henning *et al.* [63] xenotransplanted human prostate tumor into severe combined immunodeficiency (SCID) mice and then replaced water with brewed GT for 13 weeks. Tumor volume, oxidized DNA and protein damage in tumor tissue were all significantly reduced with GT consumption. Decreased expression of hypoxia-inducible factor 1- α , vascular endothelial growth factor and tumor 5-cytosine DNA methyltransferase 1 mRNA also occurred [63].

Other studies have focused on the general effect of GT beverage consumption on cancer prevention. Bettuzzi *et al.* [64] conducted a one-year double blind clinical trial on men with high-grade prostate intraepithelial neoplasia. Among the volunteers who were given catechins, only one tumor was diagnosed whereas nine cancers were detected among the placebo group. The catechin treated volunteers received significantly better scores on the international prostate symptom score and exhibited no significant side or adverse effects. However, in the 11 years of the previously discussed Ohsaki study, GT consumption did not correlate with decreased cancer related mortality [54]. Although research remains limited in human subjects, the combined (*in vitro* and *in vivo*) literature show the potential of GT to protect against oral, prostate, lung, colorectal cancer, and other target tissues. Such studies have been presented in several recently published reviews [65–67].

Table 4. Recent studies on green tea and cancer.

References	Model	Treatment	Dosage	Main outcomes
Ohga <i>et al.</i> [57]	Human cell lines A375SM and HSC3	EGCG	100 µM	EGCG selectively targeted tumor-associated endothelial cells and endothelial progenitor cells, thereby suppressing their migration.
Kato <i>et al.</i> [58]	Human cell lines HSC3, HSC4, SCC9, SCC25 and HeLa	EGCG	5, 10, 20, 50 µM	EGCG treatment partially reversed the hypermethylation status of the RECK gene.
Siddiqui <i>et al.</i> [59]	LNCaP and 22Rv1 cells	EGCG	0, 10, 20, 40, 60 µM	EGCG competitively binding to AR and interrupting the gene expression regulated by AR.
Yuasa <i>et al.</i> [61]	Tissue of gastric cancer patients	Brewed GT	0–10 cups per day	Methylation of CDX2 and BMP-2 were inversely correlated with GT intake
Thangapazham <i>et al.</i> [62]	MDA-MB-231 cell line and athymic nude mice model	EGCG and GTP	0–200 µg/ml	EGCG and GTP down regulated cancer related gene expression and inhibited proliferation of cancer cell.
Henning <i>et al.</i> [63]	Male SCID mice	Brewed GT		Tumor volume, oxidative DNA and protein damage in tumor tissue were all significantly reduced with GT consumption.
Bettuzzi <i>et al.</i> [64]	Men with high- grade prostate intraepithelial neoplasia	GT catechins	600 mg/day	One tumor was diagnosed in treatment group whereas nine cancers were detected among the placebo group. Treated group received higher score of international prostate symptom.
Kuriyama <i>et al.</i> [54]	Japanese adults	Brewed GT	<1, 1–2, 3–4, >5 cups per day	GT consumption did not significantly associate with cancer mortality.

EGCG: (–)-epigallocatechin gallate; AR: androgen receptor; GTP: green tea phenols; GT: green tea.

8. Gastrointestinal Health

The human gastrointestinal (GI) tract contains more microorganisms than any other surface of the human body with the large intestine alone containing approximately 10^{14} microorganisms [68].

Although remarkably constant within an individual over time, the microbiome can be perturbed by diseases or modulated by probiotic or prebiotic interventions [68–74]. Dietary polyphenols can also impact the GI microbiome by the time of absorption. Lee *et al.* [75] have provided extensive information on the gut microflora in response to GT extracts and their aromatic metabolites. The results showed that metabolites were produced by the bacteria after exposure to a GT polyphenol rich extract but their sensitivity towards polyphenols varied among species. The proliferation of “Good” bacteria (commensal anaerobes), which have been linked to benefits associated with host nutrition and health, were less affected by the extract but growth of pathogenic bacteria were significantly reduced. Su *et al.* [76] studied the effect of a commercial GT extract product containing 94% EGCG on three pathogenic bacteria (*Staph. Aureus* and *Strep. Pyogenes*), *E. coli*, and three probiotic bacteria (*L. acidophilus*, *B. animalis* and *L. casei*). The growth of all three pathogens was inhibited by GT at significantly lower levels (minimum inhibition concentration (MIC) of 100 µg/mL GT) compared to the three probiotic bacteria (MIC >800 µg/mL). Moreover, a synergistic effect between the probiotics and GT product was reported resulting in reduced growth of the pathogenic bacteria. The GT MIC value for *E. coli* was comparable to that of the probiotic bacteria. These results are consistent with a later study demonstrating that a GT extract inhibited probiotic bacteria and *E. coli* indiscriminately [77]. Alternatively, Molan *et al.* [78] compared two types of GT with different mineral composition. Exposure to a Chinese GT only slightly increased the growth of *L. rhamnosus* but had no effect on *B. breve*. However, the selenium-containing GT positively influenced the growth of both organisms indicating that the selenium content in GT could be a major factor in promoting probiotic bacterial growth.

9. Bioavailability

Research on the bioavailability of GT polyphenols is essential in order to understand their health promoting mechanisms. However, such studies have typically used cell models under certain digestion conditions while animal and human clinical trials remain limited. Nonetheless, Green *et al.* [79] conducted an *in vitro* digestive recovery experiment with EC, EGC, EGCG and ECG by subjecting each to a digestion protocol that mimicked the gastric and small intestinal environment. The results showed poor recovery of the pure catechins (<10%) after exposure to the digestion process. Conversely, a more recent study demonstrated that GT catechins are highly bioavailable [80]. In this study, plasma and urine samples were collected from ten healthy men before and after ingestion of 500 mL GT beverage containing 648 µmol of flavan-3-ols over a 24 h period. A $C_{\max}$ of 29–126 nM occurred in the plasma at 1.6–2.3 h ($T_{\max}$) post ingestion indicating that absorption occurred in the small intestine. Analysis of the urine samples showed 11.4% recovery of EGC and 28.5% of EC. The researchers also noted that accurate quantification of catechins bioavailability cannot be accessed solely by $C_{\max}$ and $T_{\max}$ values because flavan-3-ols metabolites rapidly circulate in the system. Roowi *et al.* [81] studied flavan-3-ols degradation in the large intestine by incubating GT-EC, EGC, and EGCG with human fecal samples. The results showed degradation of the flavan-3-ols at concentrations equivalent to 40% of the initial intake. A follow-up study completed by Calani *et al.* [82] identified GT flavan-3-ol metabolites in the urine of 20 volunteers. For the first time,

six colonic metabolites were recovered supporting the important role of colonic microbiota in the digestion of GT flavan-3-ol. The mean bioavailability was approximately 62% after 48 h.

Green tea polyphenols bioavailability can be enhanced with food additives or by ingestion through different forms. By combining a catechin extract with food additives (ascorbic acid and sucrose), Peters *et al.* [83] showed increased catechin absorption (from 61.0 pmol·h/L plasma to 181.8 pmol·h/L plasma) using a digestion/Caco-2 cell model. Henning *et al.* [84] showed increased bioavailability of GT flavonoids in healthy humans when supplemented as a capsule. In yet another study, Chow *et al.* [85] determined the oral bioavailability of GT catechins using human volunteers randomly assigned to different dose groups and administered a catechin supplement in capsule form with or without a breakfast. Analyses of tea catechin levels in plasma and urine showed that bioavailability was greater under fasting conditions.

GT phenols (either free, conjugated or bound) bioavailability is thus dependent upon the food vehicle (beverage or extract) or upon other foods consumed [86]. However, there also remains a critical lack of information on the interactions of GT catechins in the complex matrix in terms of their physicochemical properties [86]. Additionally, GT phenols, particularly the catechins, readily undergo biotransformation via methylation, glucuronidation, sulfation, and ring fission [87], which can affect their health benefiting properties, their site of absorption and multiple host related factors (e.g., gender, age, genetics, *etc.*) [88]. For more information on the bioavailability—biotransformation of phenolic based compounds, including the tea constituents, and their relationship to health, the reader is referred to other comprehensive reviews [36,86–88].

10. Conclusions

Evidence supporting the health benefits of GT intake, with an emphasis on the catechins, has been accumulating at an unprecedented rate over the past decade, including its ability to prevent or remediate inflammation, atherosclerosis, cancer, obesity and diabetes. The mechanisms by which GT may exert their effects have also been studied using different experimental designs and approaches. For example, it is widely agreed that phenols protect against cellular oxidative stress albeit no longer as free radical scavengers or chelators of redox metals but rather as cell signaling agents of endogenous responses. However, most GT antioxidative related research has been completed *in vitro*. Adding to the uncertainty of where and when GT polyphenols accumulate in or pass through the body, it is questionable that the same antioxidant effect *in vitro* will be similar to *in vivo* results. Moreover, *in vivo* studies are difficult if not impossible due to the current lack of methods to reliably measure ROS levels. By contrast, other studies have shown the GT pro-oxidant activity promotes endogenous antioxidant systems and thus increases antioxidant enzymes expression. Given that more evidence is available on the ability of GT polyphenols to modulate gene expression and cell signaling via animal and human studies, this mechanism may be more important in terms of preventing cancer, metabolic disorders, *etc.* However, more questions need to be answered: Where do GT polyphenols go? Do they stay, and for how long? How do other food matrices (such as caffeine, proteins, carbohydrates) affect the health promoting properties of GT? The choice of cell or animal models and how they relate to humans, dosages, introduction of other dietary agents and the analytical approach used should be carefully considered. Extensive meta-analysis of the existing data may aid in answering these

questions. Moreover, the effect of GT on the GI microbiome and *vice versa* cannot be ignored in the context of their seemingly symbiotic relationship. Lastly, GT catechins have received the major focus of study while other polyphenols have been largely neglected. However, as the emphasis of understanding synergisms among nutraceuticals is growing, it is expected that more studies will focus on the possible roles that GT polyphenols play in concert to protect against specific cellular stresses or diseases. Nonetheless, the current studies suggest that the GT agricultural base will continue to shift from one that produces a highly popular beverage to one that also includes GT as a potent health promoting food.

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