Short Communication

Pleiotropic Effects of Green Tea

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Abstract

Green tea (made from the leaves of *Camellia sinensis*) has been widely consumed for thousands of years and is generally recognized as a very healthy beverage. Phenolic compounds in green tea (especially epigallocatechin-3-gallate or EGCG) activate the nuclear erythroid-2 like factor-2 antioxidant response element (Nrf2/ARE) signaling system and destroy reactive oxygen species (ROS) that are unhealthy. So, green tea consumption has been linked to a decrease in overall mortality due to cardiovascular diseases in both men and women and mortality from cerebrovascular disease and respiratory disease in men. Green tea consumption was not linked to a decrease in mortality due to cancer. However, many studies have described how green tea extract can prevent several types of cancer. This apparent discrepancy could be due to the fact that over-activation of the Nrf/ARE signaling system can lead to multidrug resistant cancer. So, green tea is like many things. It should be consumed in moderation. Overconsumption of caffeine and/or EGCG in green tea extracts can be toxic to some people. Also, caffeine is an adenosine receptor antagonist. So, the amount of caffeine that is consumed by people in clinical trials for drugs that treat autoimmune diseases should be controlled, since many of them are adenosine agonists. Also, consumption of green tea may help prevent some neurodegenerative diseases, including Parkinson's disease. One way that it can do this is to increase the amount *Bifidobacterium* species in the gut. This species of bacteria can help the immune system protect against the development of inflammatory diseases. They do this by helping to digest fermentable dietary fiber.

ABBREVIATIONS

AD: Alzheimer's Disease; ARE: Antioxidant Response Element; EGCG: Epigallocatechin-3-Gallate; ER: Endoplasmic Reticulum; FDA: Food and Drug Administration; L-DOPA: L-Dihydroxyphenylalanine; LDL: Low Density Lipoproteins; Nrf2: Nuclear Factor-Erythroid 2 p45-related factor 2; ROS: Reactive Oxygen Species; UPR: Unfolded Protein Response

INTRODUCTION

Green tea made from the leaves of *Camellia sinensis* has been widely consumed for thousands of years and is generally recognized as a very healthy beverage [1]. It is second only to fresh water in popularity. Yet, like fresh water and all other substances, green tea can be toxic if consumed at too high a dose [2,3]. That is, many college-aged people who go to hospital emergency rooms are there because they drank too much water as part of their initiation into a fraternity or sorority. This can cause a heart attack, due to electrolyte imbalance. Fortunately, green tea has not become popular in such initiations, so there are no cases of toxicity due to its over-consumption as a hot, aqueous infusion. However, not everyone can tolerate the taste of green tea, so there are many dietary supplements that are green tea extracts. Many of these have been tested and found to have important health benefits [4-19]. One of them, sinecatechins 15% or Veregen®, is an FDA-approved ointment for the treatment of external genital and perianal warts caused by the human papillomavirus [20]. The active ingredients are catechins that are extracted from green tea. They are immune modulators that inhibit major viral functions. On the other hand, extracts of green tea can be toxic, especially when consumed along with energy drinks and other sources of caffeine [3,21,22].

Still, green tea has been recognized for centuries for its ability to prevent and treat many diseases, largely due to its antioxidant activity [23,24]. Modern science identified phenolic compounds as antioxidants in green tea, as well as fruits and vegetables [25]. Several *in vitro* assays are used to measure the antioxidant capacities of them [26]. This has led to many products, such as açaí and pomegranates to be labeled as "super foods", due to their high antioxidant capacities [27,28]. The antioxidants were thought to act by destroying reactive oxygen species (ROS) that are produced in normal metabolism [29]. ROS and accumulated oxidative damage were considered to be major sources of diseases caused by smoldering inflammation [29,30]. However, the idea that dietary antioxidants act by reacting directly with ROS *in vivo* is largely discredited [29]. Instead, they alter cell signaling and mitochondrial function. A recent article described how the many ingredients in green tea act synergistically to affect many enzymes in the drug-target-pathway-disease interaction network that contains six groups of target proteins [31]. However, the majority of the previous literature on the effects of green tea

polyphenols on health has focused on the nuclear erythroid-2 like factor-2 (Nrf2), a transcription factor [32-37]. It is the main regulator of cellular antioxidant defense mechanisms. It controls the expression of several antioxidant and detoxification genes. It does this by activating the antioxidant response element (ARE) in their promoter regions [38].

Effects on lifespan

In a prospective study, drinking green tea was found to be associated with a lower incidence of death due to cardiovascular in both men and women and mortality from cerebrovascular disease and respiratory disease in men [39,40]. No association was found between green tea consumption and total cancer mortality [39]. However, to the best of our knowledge, the consumption of green tea extract or dietary supplements containing green tea polyphenols was not controlled. That is, the effects of green tea might be overwhelmed by the consumption of dietary supplements that provide much higher doses of epigallocatechin-3-gallate (EGCG) than from drinking green tea. Still, green tea has been used in many parts of the world for centuries as a health tonic [1]. Epidemiological data have indicated that green tea may prevent stroke and cardiovascular diseases [1]. Many of the health effects have been attributed to the ability of EGCG to activate the Nrf2/ARE signaling pathway [33]. In addition, EGCG stimulates autophagy in vascular endothelial cells [41]. It also stimulates hepatic autophagy and lipid clearance [42]. Finally, the enhanced activity of Nrf2/ARE in naturally long-lived naked mole-rats (*Heterocephalus glaber*) may be responsible for their longer lifespan, compared to other rodents [43].

Protect against smoldering inflammation

One way that green tea polyphenols like EGCG can extend the lifespan and help prevent cardiovascular, respiratory and neurodegenerative diseases is by protecting against smoldering inflammation [30]. Even though acute inflammation is important for maintaining good health, chronic, smoldering inflammation can lead to many diseases, including autoimmune diseases, arthritis, many types of cancer as well as cardiovascular, respiratory and neurodegenerative diseases. That is, in healthy cells, mitochondria produce energy and make pro-inflammatory free radicals and ROS as by-products of the tricarboxylic acid cycle and oxidative phosphorylation. Moreover, peroxisomes oxidize fatty acids that have more than eight carbons and produce H_2O_2, which is broken down in a reaction catalyzed by the enzyme called catalase. Before it is broken down, H_2O_2 can oxidize proteins, lipids and other biochemicals. At the same time, it can act as a second messenger that can regulate several biological processes. Also, when pathogenic bacteria infect the body, immune cells kill them by causing oxidative damage and inflammation. Although there is some collateral damage to the surrounding healthy cells and tissues, this does get repaired in healthy people. However, when the immune system is overactive, it can incorrectly identify environmental chemicals, foods and even one's own cells as foreign and mount a potentially fatal autoimmune response or allergic reaction. So, inflammation, like so much else, must be carefully controlled [30].

Protection against cardiovascular diseases

One of the major risk factors for cardiovascular diseases

is obesity, or metabolic syndrome [30]. Green tea catechins, including EGCG may be able to help prevent metabolic syndrome from developing [44]. Green tea catecins lower the concentration of LDL-cholesterol in blood [45]. Also, green tea extract was able to cause significant weight loss, reduce waist circumference, and decrease the concentrations of total cholesterol and low density lipoproteins (LDL) in blood plasma without any adverse side effects in obese women [45]. It was suggested that this was at least partly due to inhibition of Ghrelin secretion, leading to increased adiponectin concentrations [45]. Ghrelin and adiponectin are protein hormones produced by the hippocampus and adipose cells [30]. Ghrelin increases the amount of food intake and fat mass while activating the reward network (mesolimbic system) of the brain. Adiponectin is anti-inflammatory and anti-atherogenic. It stimulates the appetite and its concentration increases during starvation [30]. Also, obesity can damage the endoplasmic reticulum(ER) and lead to the unhealthy accumulation of mis folded proteins [46]. This is a form of intracellular stress that occurs whenever the protein-folding capacity of the ER is over whelmed. This can lead to reduced blood flow, cardiac hypertrophy and heart failure. ER trans membrane sensors are supposed to detect the accumulation of unfolded proteins. They should activate transcriptional and translational pathways that deal with unfolded and mis folded proteins. This is known as the unfolded protein response (UPR). If the UPR fails to control the concentration of unfolded and mis folded proteins in the ER, apoptotic signaling is induced. Furthermore, oxidative stress and subsequent cellular damage can damage the myocardium after ischemia/reper fusion and in cardiac hypertrophy secondary to pressure overload. To help prevent this oxidative stress, there are antioxidant defense systems that should ensure that the response to oxidants is adequate. Nrf2 is closely linked to the UPR sensor called pancreatic endoplasmic reticulum kinase. Interventions against ER stress that activate Nrf2 can reduce myocardial infarct size and cardiac hypertrophy. Finally, activating the Nrf2/ARE pathway may be of importance in ischemic preconditioning, in which the heart is subjected to one or more episodes of nonlethal myocardial ischemia-reperfusion before the sustained coronary artery occlusion [44]. It has also been shown that EGCG can protect against oxidative stress that is caused by cerebral ischemia by activating the Nrf2/ARE signaling pathway [37]. It also acts as a mechano sensitive transcription factor that can protect endothelial cells from fluid shear stress that can lead to stroke and other cardiovascular diseases [47].

However, Nrf2 can have a detrimental effect on the heart when autophagy is impaired [48]. That is, cells and proteins are continuously being broken down in a process called autopoeisis [2]. One mechanism of autopoeisis is autophagy, in which unnecessary or dysfunctional proteins, organelles and cells are degraded. When autophagy is impaired in the heart, the Nrf2/ARE signaling pathway can become dysfunctional, leading to heart damage [48]. So, the relative physiological effects of green tea and extracts enriched in EGCG can depend on the health of the individual.

Protect against neurodegenerative diseases

As mentioned previously, the phenolic compounds (especially EGCG) are antioxidants that can help prevent

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smoldering inflammation that can lead to cardiovascular and neurodegenerative diseases [29,30]. In general, phenolic compounds in foods may be able to help prevent cognitive and neurodegenerative disorders from developing [24,49,50]. Moreover, epidemiologic evidence suggests that green tea may help prevent stroke [1]. However, the tendency to think of individual diseases in a reductionist manner can be misleading [2,30,51]. Many diseases are linked with each other, leading many researchers to study their interactions in a disease-ome, similar to the genome, metabolome and other –omics [51]. That is, neurodegenerative and cardiovascular diseases can be caused by the complications that emerge due to metabolic syndrome [30,51]. One of the complications is that the composition of bacteria in the gut is quite different in obese people than in those who aren't [30]. So, it is important to note that drinking green tea can cause an increase in the relative amount of *Bifidobacterium* species that are in the gut [52]. The composition and function of the intestinal microbial flora change when people become obese [53]. One of the changes is that barrier-protective bacterial species (*Bifidobacterium* species) decrease and endotoxin-producing species (*Desulfo vibrionaceae*) increase [54,55]. *Bifidobacterium* species also help the immune system protect against the development of inflammatory diseases. They do this by helping to digest fermentable dietary fiber [30]. So, the gut microbiome can affect the central and enteric nervous system and influence behavior [56-58]. There is bidirectional signaling between the gastrointestinal tract and the brain, mainly through the vagus nerve. This microbiota–gut–vagus–brain axis helps maintain homeostasis and may be involved in the etiology of several metabolic and neurodegenerative diseases [59]. The interactions between the gut and the brain are affected by the micro biota in the through immunological, neuroendocrine and neural mechanisms [60]. They may be important in Parkinson's disease, too. Improper regulation of this axis has been associated with gastrointestinal disorders that often occur prior to the onset of shaking, rigidity, slowness of movement and difficulty in walking. Also, excessive stimulation of the innate immune system due to an unhealthy distribution of bacteria in the gut and/or small intestines can lead to increased permeability of the intestines. This can cause smoldering inflammation. At the same time, activated enteric neurons and enteric glial cells can contribute to the mis folding of α-synuclein protein, which is a hallmark of Parkinson's disease. In addition, the adaptive immune system may be disturbed by bacterial proteins that interact with human antigens [60]. The phenolic compounds in green tea may help prevent the smoldering inflammation.

However, the caffeine in green tea may also help prevent Parkinson's disease [61]. Caffeine binds to the A2A adenosine receptor, as does the prescription drug is trade fylline. However, the data from Phase II clinical trials did not include data on caffeine consumption. So, it could be very important to control or at least monitor caffeine consumption during clinical trials for drugs that act by binding to adenosine receptors [61,62]. This is also true for adenosine agonists and antagonists that are being tested for treating autoimmune diseases [63]. There is another possible link between caffeine consumption and Parkinson's disease. Overconsumption of the fruit called graviola (*Annona muricata*) has been linked to an atypical form of Parkinson's

disease that does not respond to the standard treatment with L-dihydroxyphenylalanine (L-DOPA) on the Pacific islands of Guam and New Caledonia as well as the island of Guadeloupe in the French Caribbean [64]. However, graviola and other fruits in the Annonaceae family are also widely consumed in Brazil and many parts of Asia, even though there have been no reports of atypical Parkinsonism there [65]. It is possible that the widespread consumption of green tea and coffee may be a factor in preventing it. However, overconsumption of caffeine can be toxic and even fatal [66].

EGCG may also promote neural progenitor cell proliferation by activating the sonic hedgehog signaling pathway during adult hippocampal neurogenesis [67]. That is, the hippocampus is the one part of the brain where new neurons are produced in adults [2,30]. This process may be promoted by EGCG that is in green tea.

Antiviral and Antibiotic effects

As mentioned previously, there is a green tea extract (sinecatechins 15% or Veregen®) that has been approved by the FDA for treating external genital and perianal warts caused by the human *papilloma virus* [20]. Also, a catechin enriched green tea extract had bacteriostatic effects in all the bacteria isolates tested and inhibitory effects on *influenza virus* A3 (H3N2) and *coxsackie virus* B4 [6].

Protect against skin diseases

Skin is the largest human organ [68]. It is constantly being exposed to exogenous and endogenous toxins and ROS. So, green tea may help protect the skin from UV radiation [23].One of the defense mechanisms is the Nrf2/ARE signaling system [68]. So, EGCG and other phenolic compounds in green tea help protect the skin from damage due to ROS. However, some ROS also act as biochemical signals that help regulate important cellular processes such as signal transduction, gene expression, and apoptosis. So, ROS can have both beneficial and detrimental effects [68].This is especially important in multidrug resistant cancer.

Effects on cancer

Even though epidemiological evidence indicated that green tea extract does not decrease overall mortality due to cancer [39], there are several studies that indicated that it may help prevent and even treat several types of cancer [1,49,69-73]. One way that it may be able to prevent cancer is by preventing angiogenesis [69]. That is, healthy people can have microscopic tumors and remain asymptomatic. Only after the cancer grows and spreads (metastasize), does it become deadly. To grow and metastasize, new blood vessels need to be formed and this is called angiogenesis. If this can be prevented, it could prevent cancer. So, Polyphenon E is being evaluated in some clinical trials for treating prostate, bladder, esophageal, lung, head and neck cancers, as well as leukemia, and is already commercially available as a topical ointment [69].

So, green tea and the phenolic compounds (especially EGCG) in it may be able to prevent and even help to treat many types of cancer by activating the Nrf/ARE signaling system [1,49,69-

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73]. However, when over-activated, the cancer cells may become resistant to many drugs used in chemotherapy [70]. It should be noted that there are other biochemical that are widely assumed to be completely healthy (such as resveratrol in red wine and *sulforaphane* in broccoli) because they activate the Nrf2/ARE system [74]. However, if they or EGCG are over-consumed as dietary supplements by patients who are starting chemotherapy, it could lead to multidrug resistant cancer and death. Still, one should remember that cancer is not a monolithic disease, but actually several different diseases [30]. Even cancers that affect the same organ (such as the breast) can have very different causes, treatments and prognosis [30]. Finally, more research is needed to establish just how much EGCG and other supposedly healthy compounds are needed to over-activate the Nrf2/ARE and cause multidrug resistant cancer.

Toxicity

In addition to possibly being able to cause multidrug resistant cancer, green tea extracts can be toxic in other ways. Moreover, all substances are toxic if over-consumed or given to the most susceptible organ [2, 30]. That is, the dose is the poison. As a result, even fresh drinking water is toxic when over-consumed, often as an initiation into a fraternity or sorority. If electrolytes are depleted, it can lead to cardiac failure [2,30]. However, to the best of our knowledge, no organization has ever forced people to over-consume green tea as part of an initiation. Moreover, the caffeine in green tea is a diuretic, so it increases the production of urine. This may help limit the bioavailability of EGCG and caffeine. Moreover, if one drinks green tea it may leave less room in the stomach for other foods, thus limiting caloric intake. So, it is quite unlikely that green tea is toxic. Even if cancer patients are starting chemotherapy, the effects on suppressing the appetite will probably keep them from over-consuming it. However, they or their caregivers may read about the potential health effects of green tea extracts and especially EGCG. So, they might think that they should consume dietary supplements enriched in EGCG or even pure 100% EGCG. Moreover, many think that if a little bit of something is healthy then more of it may be even healthier. This could lead to over-consumption and multidrug resistance. Still, more research is needed to determine which cancers are susceptible to developing multidrug resistance through over-activation of the Nrf/ARE system and what doses of EGCG (or resveratrol) are needed to cause toxicity.

For people who don't have cancer, there is still another potential toxicity of green tea extract - caffeine. It can be toxic at high doses, so some green tea extracts are decaffeinated [66,75]. However, it is usually safe when consumed in moderation (500 mg or less daily) and may even help protect against Parkinson's disease [61,66].

CONCLUSION

Green tea consumption has been linked to a decrease in overall mortality due to cardiovascular diseases in both men and women and mortality from cerebrovascular disease and respiratory disease in men. It was not linked to a decrease in mortality due to cancer. However, many studies have described how green tea extract can prevent several types of cancer. This apparent discrepancy could be due to the fact that over-activation

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