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The beneficial effects of green tea on human health: An updated review

Mir Monir Hossain, Shahrin Mahmood and Tasmuna Tamrin Tanmy

Abstract
Green tea is un-fermented product of *Camellia* species. The leaves of both *Camellia sinensis* and *Camellia assamica*, are used for the production of green tea, but *C. assamica* is mainly used for the production of black tea. Green tea is widely produced from the leaves of *C. sinensis*, now a day's which is one of the most popular beverages worldwide. Over the past 50 years or more, scientists have studied this plant with respect to potential health benefits. Research has shown that the main components of green tea that are associated with health benefits are the catechins. The four main catechins found in green tea are: (-)-epicatechin (EC), (-)-epicatechin-3-gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin-3-gallate (EGCG). Of these four, EGCG is present in the largest quantity, and so has been used in most of the researches. Among the important health benefits of green tea are: anticarcinogenic, anti-inflammatory, antioxidant, and antimicrobial properties, and benefits in cardiovascular disease and oral health. Research has been carried out using various animal models and cells lines, and is now more and more being carried out in humans. This type of research will help us to better understand the direct benefits of green tea. This review will focus primarily on researches conducted on human subjects to investigate the health benefits of green tea.

Keywords: Greentea, anticancer, anti-inflammatory, antimicrobial, antioxidant, cardiovascular disease, oral health, metal ions

1. Introduction
Green tea, native to China, India and Bangladesh, has been consumed and hailed for its health benefits for centuries globally. Tea is the most consumed beverage in the world behind water. However, 78 percent of the tea consumed worldwide is black and only about 20 percent is green. All types of tea, except herbal tea, are brewed from the dried leaves of the *C.sinensis* bush. The level of oxidation of the leaves determines the type of tea. Green tea is made from unoxidized leaves and is one of the less processed types of tea. It, therefore contains the most antioxidants and beneficial polyphenols. Cultivation of tea plants is economically important in many countries, and is known to be grown in as many as 40 countries. *C. sinensis* grows best in certain tropical and subtropical regions [1]. There are four main types of tea produced from this same plant, depending on how the tea leaves are processed. These teas are white, green, Oolong, and black tea. White tea is produced from very young leaves and buds that have not yet turned green, and the only processing is drying. Green tea is produced from mature leaves with minimal processing (only drying). Oolong tea is produced from partially fermented mature leaves, and black tea is produced from fully fermented mature leaves [1,2]. Green tea, which makes up around 20% of tea production worldwide, is consumed most often in China, Korea, India, Bangladesh and Japan. Oolong tea is consumed most in China and Taiwan. Black tea (around 78% of tea production) is mostly consumed in the United States and the United Kingdom. Black tea contains up to three times the amount of caffeine as green tea [3–5]. Like other drugs or nutrients within our system, the health beneficial effects of green tea solely depend on bioavailability after its consumption. In recent years, the health benefits [6]of consuming green tea, including the prevention of cancer [7] and cardiovascular diseases [8], the anti-inflammatory [9], antiarthritic [10], antibacterial [11], antiangiogenic [12],antioxidative [13], antiviral [14], neuroprotective [15], andcholesterol-lowering effects [16] of green tea and isolated green tea constituents are under investigation. However, adding green tea to the diet may cause other serious health concerns.The risk of the tea catechins can affect iron absorption, particularly in group of people who have iron deficiency. Green tea ingestion over a long period does not affect the apparent absorption of copper, whereas it decreases that of zinc and increases that of manganese. However, catechin intake does not affect the blood plasma concentration of these ions. Green tea catechins have the potential to affect absorption and metabolism of ions because flavonoids interact with a variety of metal ions.

1.1 Phytochemical Constituents

The active components of green tea that are the most health-promoting relevant medically are the polyphenols, with the flavonoids being the most important. The most pertinent flavonoids are the catechins, which make up80%–90% of the flavonoids, and approximately 40% of the water-soluble solids in green tea [17–19]. The amount of catechins in the tea can be affected by which leaves are harvested, how the leaves are processed, and how the tea is prepared. In addition, where the leaves are grown (geographically) and the growing conditions affect catechin amounts [20–23]. Polyphenols are quickly oxidized after harvesting due to the enzyme polyphenol oxidase. To prevent loss of the polyphenols, green tea leaves are heated rapidly (most commonly by steaming or pan frying) to inactivate polyphenol oxidase. Black tea leaves are dried, then rolled and crushed, which promotes oxidation. Therefore, black tea has far fewer active catechins than green tea. Green tea contains four main catechins: (-)-epicatechin (EC), (-)-epigallocatechin (EGC), (-)-epicatechin-3-gallate (ECG), and (-) epigallocatechin-3-gallate (EGCG). The most abundant of these in green tea is EGCG, which represents around 59% of total catechins. The next most abundant is EGC (around 19%), then ECG (around 14%), and EC (around 6%).

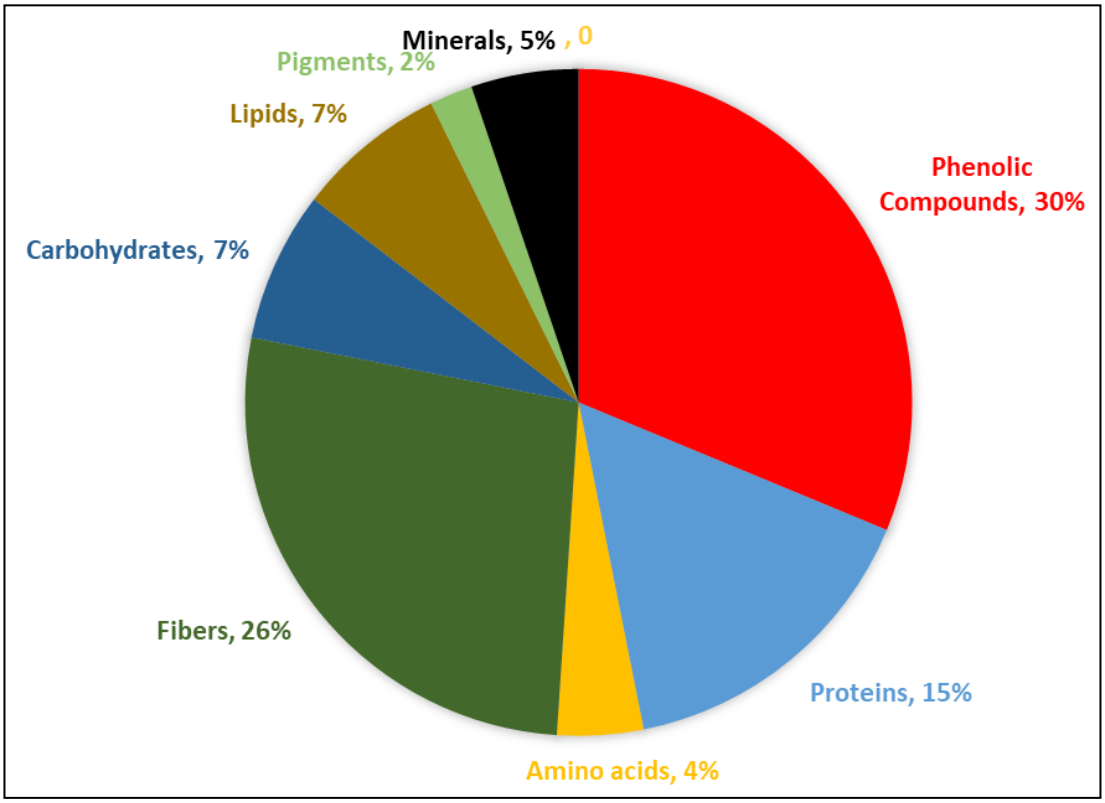

Fig 1: Chemical composition (%) of green tea [24]

The chemical composition of green tea is made up of 15-20% protein, 1-4% amino acids, 30% phenolic compounds, 7% lipids, 7% carbohydrates, 26% fibers, 5% minerals and 2% pigments on a dry weight basis[24] (See Fig 1). Amino acids like glutamic acid, tryptophan, glycine, serine, aspartic acid, tyrosine, valine, leucine, threonine, arginine, and lysine and carbohydrates (5-7% in dry weight basis) such as cellulose, pectins, glucose, fructose, sucroseare partly included in green tea [25]. Other green tea-compounds with interest in human health such as fluorine, caffeine, trace elements such as chromium and manganese [26]. It contains trace elements in lipid form (linoleic acid, alpha-linolenic acid), sterols (stigmasterol), vitamins (B, C, E), xanthine bases (caffeine, theophylline), pigments (chlorophyll, carotenoids), volatile compounds (aldehyde, alcohol, esters, lactones, hydrocarbons).

1.2 Processing of tea leaves

The green and black teas are the products of thesame plant, but the basic difference lies in their processing. Black tea is the fermented product andundergoes fermentation process before drying, Whereas, black tea is made by oxidation process. Afterplucking, leaves are subjected to the process of withering (removal of moisture by air flow), preconditioning, fermentation and drying which areinvolved to make a finished product [27]. The color oftea leaves changes after all the steps from green tocopper brown and gives a floral smell. The leaves are heated immediately, mechanically wound, compressed and then shade dried to preserve theirnatural components and color.

2. Green tea processing

The vital steps of green tea processing are as below:

Fresh leaves collection → sorting and cleaning → withering (often) → panfrying or steaming → drying.

The discrete features of green tea processing isthat, the leaves are never subjected to fermentationprocess. Instead, the leaves are steamed (95-100ºC) for 30-45 seconds immediately after harvesting, toinactivate the enzymes and protect degradation ofvitamins. For this reason, the green tea contains morevitamin contents in comparison to black tea. Thefresh leaves contain 78-80% polyphenols, whichdecreases to about 10% during rolling process. Thedrying process is crucial to preserve the aroma andstorage capacity.

3. Black tea processing

The major steps of black tea processing can be shown as follows:

Fresh leaves collection → Withering → Rolling by tea roller or CTC (crushing, tearing, curling) → Fermenting → Drying
After following these steps, the fermentation step plays a crucial role in maintaining quality of blacktea. The oxidation process predominantly oxidizes the catechins present in tea leaves. The moisture content in the tea leaves is evaporated and leaves become flaccid. The black tea is made by a CTC machine. In many countries such as India, Kenya and Sri Lanka, CTC process of tea making are being followed. But, China follows its traditional "orthodox rollers" process. For the fermentation of black tea, warm temperature (25-35ºC) and high humidity (~95%) are required. The fermentation process depends on the variety of plant and age of tea leaves. It takes half hour to three hours to complete the fermentation process. Generally, CTC machine takes less time (30 to 60 minutes), while orthodox roller takes 2-3 hours.

4. Anticancer properties

Now days, cancer is a major cause of morbidity and mortality worldwide. Billions of dollars have been poured into cancer research over the past 60 years, and still we do not seem to be any closer conclusion to actually curing it. In addition, quite often the chemotherapies do as much, if not more damage to the patient as the disease. Because cancer appears in so many different forms inmultiple parts of the body, it has been difficult to determine the mechanisms that lead to the disease. Even with what we now know about cancer risk factors, there are still many people who seemingly have none of the risk factors, and yet succumb to a rapidly aggressive form. Encouraging people to think about how a healthy lifestyle can prevent disease is certainly a step in the right direction, and it would be most helpful to identify substances that could be useful in prevention and treatment. Green tea is an exceptional cancer-preventive prescription with two features as refreshment and medication. Herbal remedies, including green tea, are the same old thing, yet by presenting the idea of malignant growth counteractive action that green tea spares individuals' lives. The supremecomponent of green tea that has been studied in cancer research is EGCG. There areseveral cancer related mechanisms attributed to EGCG. These include: inhibition of angiogenesis, DNA hypermethylation, NF-kB, telomerase activity, and tumor cell proliferation and metastasis; inductionof tumor suppressor genes; and promotion of tumor cell apoptosis [28–32]. Inhibition of angiogenesisis suggested to occur through a decrease in RNA and peptide levels of vascular endothelial growthfactor (VEGF), and by disrupting the dimerization of VEGF with the vascular endothelial growth factorreceptor 2 (VEFR2) [33]. Another suggested way in which green tea catechins may generally inhibitcarcinogenesis is through increasing levels of glutathione *S*-transferase pi (GST-pi), which catalyzesdetoxification reactions that inhibit carcinogen-induced DNA damage [34].Analysis of studies performed by using human oral consumption of green tea to assess cancer risk showed that case-control studies gave the most consistent results and were positive for reduced cancer risk in breast, cardiac, colorectal, esophageal, gastric, lung, ovarian, pancreatic, and prostate cancers [35,36]. A recent large study showed a relationship between breast cancer risk and tea consumption, with the risk being highest in the groups that did not consume tea and lowest in the groups that consumed the most cups per day. Number of cups were assessed in five categories (0.1–1.0 cups, 1.1–2.0 cups, 2.1–3.0 cups, 3.1–5.0 cups, >5.0 cups) [37]. Analysis of the types of green tea beverage or extracts used in studies suggests that green tea beverage or a supplement containing mixed catechins may be more effective than using single catechin (e.g., EGCG) supplements [38].The potential molecular mechanisms and targets that might explain how green tea catechins possess anticarcinogenic properties have been widely studied (using various cell cultures, etc.), especially in breast cancers. These include interaction with specific proteins, anti-angiogenesis mechanisms, targets for inhibition of enzyme activities and cell signaling pathways, and induction of cell cycle arrest and apoptosis [39]. The mushrooming area of nanotechnology has led to the development of potential chemotherapy involving nanoparticles (NPs). Various particles (e.g., gold) can be used to deliver compounds to specific areas of the body. Research using EGCG and nanoparticles has already begun using a number of delivery approaches. These include: coating an NP, such as gold, with EGCG; use of encapsulated (in liposomes or polymeric NPs) EGCG in NPs along with anti-cancer drugs, outer ligands that will bind to specific targets, or outer polymers that will enhance the intestinal absorption of EGCG [32].

5. Cardiovascular disease (CVD) health benefits:

At present, Cardiovascular disease (CVD) is a leading cause of death and a complex disorder involving multiple factors. The factors those involve in CVD are: inflammation, oxidative stress, platelet aggregation, obesity and lipid metabolism. Some of these factors are also involved in other disease processes but will be discussed in this paper under CVD. There have been a number of studies over the years assessing green tea consumption in respect to CVD risk [40]. Very recently, two studies from Japan that included nearly 50,000 people found a decreased mortality rate due to CVD based on consumption of various numbers of cups per day. One study showed a 28% decrease in CVD death between those who consumed ≤ 3 cups and those who consumed more than ≥ 10 cups. The other study showed a 14% decrease in CVD mortality between those who consumed <1 cup and those who consumed ≥ 5 cups [41,42]. In Japan, Other studies using a green tea extract found that, after 12 weeks, the subjects had reductions in body fat (10%), blood pressure (6.5%), and low-density lipoprotein (LDL) levels (2.6%), suggesting reduced risk of CVD. After two months, diabetic patients also had reduced fasting blood glucose levels (from 135 to 128.8 mg/dL), and hemoglobin A1c (HBA1c) levels (from 6.2% to 6.0%) [43,44]. A large meta-analysis of 17 studies from over 30 years, including data from Europe, the UK, and the U.S., found that increasing consumption of green tea by three cups per day decreased the risk of myocardial infarction (MI) death by 11% [45]. Another study showed a decreased risk of mortality in patients who had an acute MI and a history of regular green tea consumption for at least a year prior to the MI. Participants who did not drink green tea had a 14% rate of death due to the MI; participants who drank up to 14 cups per week had an 11% rate of MI death; and participants who drank more than 14 cups per week had a 10% rate of MI death [46]. An interesting study in patients with CVD showed that consumption of EGCG resulted in a rapid improvement of vascular endothelial function. Participants who ingested an initial dose of 300 mg of EGCG had an improved brachial artery flow-mediated dilation from 7.1% to 8.6% after 2 h [47]. Another recent study found that increased intake of dietary flavonoids was associated with a decreased risk of CVD. The participants were divided into three groups based on average daily consumption of flavonoids. The first tertile consumed 89 mg/day, the second tertile consumed 251

mg/day, and the third tertile consumed 532 mg/day. The number of deaths due to CVD in the first tertile was 8.6%; in the second tertile, 6.4%; and in the third tertile, 5.0% [48].

5.1. Inflammation

Rather than the CVD, inflammation is also involved in arthritis, aging, cancer, etc. Many of the anti-inflammatory effects when using green tea have been studied in rheumatoid arthritis (RA) and osteoarthritis (OA), and are pertinent to CVD as well. Some general anti-inflammatory mechanisms of green tea components are: increased production of the anti-inflammatory cytokine, IL-10; regulation of IL-6 synthesis and signaling; decreased production of destructive matrix metalloproteinases via TNF-α induced phosphorylation of mitogen-activated protein kinases (MAPKs); and decreased expression of the chemokine receptor CCR2 and decreased levels of the proinflammatory cytokines IL-1β and TNF-α [49–52].The specific studies on inflammation can be roughly categorized into: inhibition of neutrophil-endothelium interaction, modulation of neutrophil functions and death, and regulation of inflammation factors. Neutrophil migration and function are an integral part of the inflammatory response, so controlling neutrophils is vital in decreasing inflammation. Studies have shown that green tea catechins cause a reduction in the number of leukocyte-endothelial cell adhesion molecules (CAMs), such as ICAM-1, VCAM-1, and E-selection, expressed on the endothelial cell surface. This restricts the ability of the neutrophils to migrate to sites of infection [53,54]. Other studies have shown that factors known to regulate neutrophil function, such as IL-1 β, IL-2, TNF-α, and granulocyte-macrophage colony-stimulating factor (GM-CSF), are suppressed by consumption of green tea or EGCG, resulting in inhibition of inflammation [55–57]. Studies on the inhibition of pro-inflammatory factors have shown that green tea catechins downregulate many inflammatory chemokines, cytokines, and inflammatory markers such as: IL-1α, IL-1β, IL-6, IL-8, Interferon gamma (INF-ϒ), and C-reactive protein (CRP) [56,58–60].

5.2. Oxidative Stress

Oxidative stress in the body is closely connected to inflammation and CVD, and is the result of the damaging effects of reactive oxygen species (ROS). These ROS are capable of causing chronic inflammation through induction of inflammatory cytokines and chemokines, and pro-inflammatory transcription factors. In general, green tea catechins have been found to have antioxidant activity through: inhibiting redox sensitive transcription factors and pro-oxidant enzymes, scavenging ROS, and inducing anti-oxidant enzymes.

Studies to determine the antioxidant capabilities of green tea may measure a variety of substances. Tests may measure the presence of known ROS or their metabolites, such as hydroxyl radical, peroxides, superoxide, and singlet oxygen. Other measurements may be for known antioxidant substances such as superoxide dismutase (SOD) and glutathione peroxidase, or substances that indicate inflammation such as high-sensitivity C-reactive protein (hs-CRP) and TNF-α. Another type of testing assesses total antioxidant capacity (TAC), also known as total antioxidant status (TAS), which measures the amount of oxidants that are neutralized in the body (e.g., moles of oxidant neutralized by 1 L of plasma), with a lower number translating into a higher risk of disease [49].The results from recent studies have shown that green tea catechins can affect levels of ROS [61–64], increase levels of antioxidants [65–68], decrease levels of inflammatory substances [69,70], and increase TAC (TAS) [66,68,69]. An excellent summary of earlier studies that measured ROS and TAC can be found in a chapter by Serafini *et al*. 2011 [49].

The antioxidant activity of green tea polyphenols is predominantly due to the combination of aromatic rings and hydroxyl groups, which synthesize their chemical structure and consequently bind and neutralize lipid-free radicals by these hydroxyl groups. Numerous researches have been exhibited in different aspects on antioxidant activity of green tea polyphenols which are exceptional electron donors and are effective scavengers of physiologically reactive oxygen species (ROS) *in vitro*, including superoxide anions [71].

Consequently, green tea is the most effective against beta-carotene oxidation as far as the antioxidant property is concerned and can serve as a natural source of free radical scavengers and cancer prevention agent [72]. The most potent antioxidant polyphenol of green tea is EGC. Again, radical scavenging is high in the gallocatechin including EGCG and EGC. Many studies have been reported on green tea that has much higher antioxidant activities against free radicals which are not found in vegetables. It is measured mainly by the Oxygen Radical Absorbance Capacity (ORAC) assay, DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging assays and Trolox equivalent antioxidant capacity (TEAC) assay (See Fig 2) [13, 73-74].

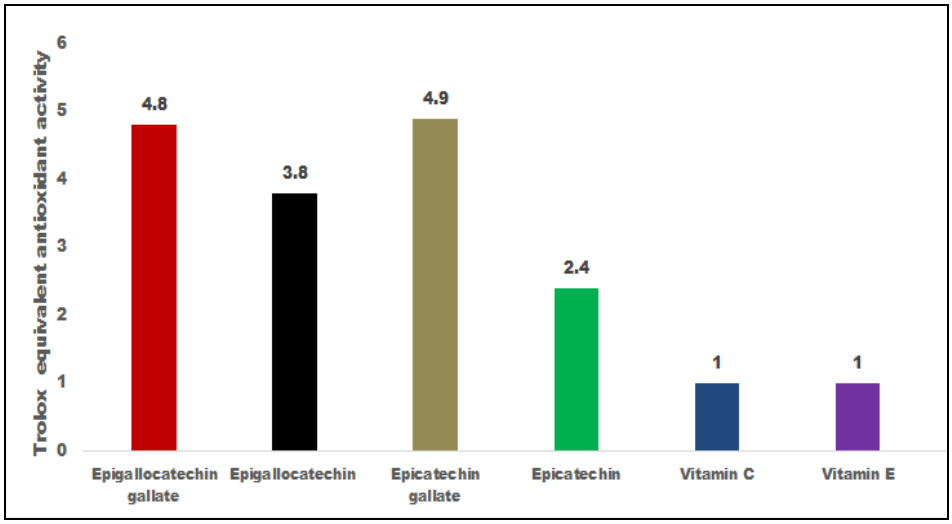

Fig 2: Reactive antioxidant properties of green tea [73].

5.3. Platelet Aggregation

Platelet activation and subsequent aggregation play an important role in CVD. When the vascular endothelium is damaged, platelets usually respond rapidly and aggregate to form plugs at the damage site, and may also form clots that could lead to vessel occlusion [75]. Many of the studies on platelet aggregation have been carried out using various animal platelets. In addition to showing that green tea catechins were involved in inhibition of platelet aggregation, studies suggested that, catechins may affect several cellular targets that are related to platelet activation, including: through the arachadonic acid pathway, inhibition of a cytoplasmic increase in calcium, decreased thromboxane A_2 (TXA_2) production, and inhibition of cyclooxygenase-1 (COX-1)) [76–79]. A study using human platelets concluded that EGCG was able to inhibit platelet activation by adenosine diphosphate (ADP) stimulation, and suppressed the p38 MAPK phosphorylation of heat shock protein 27 (HSP27), which would inhibit the release of pro-thrombotic contents from platelets [80].

5.4. Lipid Metabolism

Increased blood lipid levels have long been suspected as an increased risk for CVD, especially LDLs [81]. One mechanism that is linked with atherosclerosis is the presence of oxidated LDL [82]. There have been many studies performed using human subjects to determine the effect of green tea catechins on lipids. The studies have reported that consumption of green tea catechins lowers total cholesterol and LDL levels and also reduces blood pressure [83–90]. In addition, a recent study found that green tea catechins are incorporated into LDL particles, and are then able to reduce the oxidation of LDL. Catechins prevent LDL oxidation via radical-trapping abilities and act as hydrogen donors to α-tocopherol radicals [91].

6. Antimicrobial action

Resistance to antimicrobial agents has been becoming harmful to the environment and accelerating the global problem [92]. Nowadays many antimicrobial drugs cannot destroy their pathogenic microorganisms as they are becoming resistant. Therefore, researchers are finding some new drugs from mangrove species to control the pathogens due to the presence of antimicrobial compounds [93, 94]. The antimicrobial activity of tea was first established almost 100 years ago[95,96]. Green tea exhibits antimicrobial properties, which are ascribed predominantly to its polyphenols [97]. The degree of animation depends on the bacterial species and the polyphenol structure [98, 99]. Good evidence suggests that the catechin components of green tea are responsible for the observed antibacterial activity owing to the presence of EGC, EGCG, and ECG constituents [100, 101]. Gram-negative bacteria seem to be more resistant to polyphenols than Gram-positive bacteria, due to differences in the exterior membrane [102]. The main components responsible for the antimicrobial activity are EGCG and EGC. EGCG at 10–100 μm has shown to reduce *E. Coli* growth by approximately 50% [103]. The mechanism of antiviral action of polyphenolic compounds is based on various capacities to go about as antioxidant agents, to inhibit proteinaceous enzymes, to disrupt cell membranes, to avoid viral binding and penetration into cells, and to trigger the host cell. EGCG hinders infections by direct authoritative to biological molecules and persuades agglutination of the flu infection preventing their adsorption to target [104]. The antiviral mechanism of EGCG has been analyzed against endemic HBV (Hepatitis B virus) infection [105, 106]. Many reports demonstrated that green tea catechin, EGCG is the most active compound against HIV infectious diseases [107]. Furthermore, the evaluation has also been done with herpes simplex virus (HSV) and bovine coronavirus (BCV) to realize the resistance power of antiviral activity and therapeutic efficiency of catechin polyphenols [108].

7. Oral Health Benefits

Recently, research has launched to focus on the effects of green tea on oral health. Two of the general ways in which green tea consumption helps oral health are due to its anti-inflammatory properties, and antimicrobial activity against mouth flora such as *Streptococcus mutans* [109, 110]. The antimicrobial activity may also be responsible for the improvement observed as to bad breath [111]. The two major types of effects on oral health are a decrease in periodontist and dental caries.

7.1. Periodontitis

Green tea consumption has been found to result in decreased tooth loss,and prevent the development and progression of periodontitis. Green tea consumption also has positive effects on periodontal health when assessed as to probing depth, attachment loss, gingival bleeding, and dentin erosion. In addition to the antimicrobial effects on the main bacteria involved in gingivitis, Porphyromonasgingivalis, EGCG has been shown to inhibit the ability of the bacteria to bind to oral epithelial cells via fimbriae, and has also been shown to inactivate bacterial collagenases. EGCG also inhibits production of matrix metalloproteins and IL-8, which are responsible for initiating tissue destruction [109,110,112,113].

7.2. Dental Caries

Prevention of dental caries is attributed to the ability of EGCG to bind and inhibit salivary and bacterial amylases, in particular, α-amylase. EGCG also prevents generation of acid from carbohydrates through inhibiting the transcription and function of LDH. One of the main things that encourages tooth decay is that the major oral bacteria (e.g., Streptococcus mutans) form a biofilm on the surface of teeth. EGCG inhibits the adherence of the bacteria to teeth, decreases biofilm formation, and inhibits the ability of the bacteria to produce an acid environment. EGCG also inhibits the hydrogen binding and hydrophobic interactions of bacterial collagenases. Consumption of green tea has also been associated with an increase in oral peroxidase activity [113–115].

8. Effect on diabetes

A study by Waltner-Law *et al*. [116] provided compelling *in vitro* evidence that EGCG decreases glucose production of H4IIE rat hepatoma cells. The investigators showed that EGCG mimics insulin, increases tyrosine phosphorylation of the insulin receptor and the insulin receptor substrate, and reduces gene expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase. Recently, green tea and green tea extracts were demonstrated to modify glucose metabolism beneficially in experimental models of type II diabetes mellitus [117]. In addition, EGCG ameliorates cytokine induced beta cell damage *in vitro* [118] and prevents the decrease of islet mass induced by treatment with multiple low doses of streptozotocin *in vivo* [119].

9. Effect on obesity

The effects of green tea on obesity have received increasing attention. Tea catechins, especially EGCG, appear to have

anti-obesity [120]. African black tea extract has been shown to suppress the elevation of blood glucose during food intake and reduce the body weight in KK-A(y)/TaJcl diabetic mice [121]. Although few epidemiological and clinical studies have shown the health benefits of EGCG on obesity and diabetes, the mechanisms of its actions are emerging based on various laboratory data. These mechanisms may be related to certain pathways, such as through the modulations of energy balance, endocrine systems, food intake, lipid and carbohydrate metabolism, and redox status [122].It has been reported that the body weights of rats and their plasma triglyceride, cholesterol, and low-density lipoprotein cholesterol were significantly reduced by feedings of Oolong, black, and green tea leaves to the animals. When fed to mice, EGCG purified from green tea decreased diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation [123]. The increased and prolonged sympathetic stimulation of thermogenesis by the interaction between polyphenols and caffeine could be of value in assisting the management of obesity [124]. Recent data from human studies indicate that the consumption of green tea and green tea extracts may help reduce body weight, mainly body fat, by increasing postprandial thermogenesis and fat oxidation. These findings suggest that, EGCG alone has the potential to increase fat oxidation in human and may thereby contribute to the anti-obesity effects of green tea. However, more studies with a greater sample size and a broader range of age and body mass index (BMI) are needed to define the optimal dose [125].

10. Effects on absorption of metal ions

Green tea's catechins can affect iron absorption, particularly in groups at risk of iron deficiency [126, 127] but their effects on other ions are poorly understood. Green tea ingestion over a long period does not affect the apparent absorption of copper, whereas it decreases that of zinc and increases that of manganese [128]. However, catechin intake does not affect the plasma concentration of these ions [129]. Green tea catechins have the potential to affect absorption and metabolism of ions because flavonoids interact with a variety of metal ions [130].

11. Effects on drug-metabolizing enzymes

Long-term ingestion of green tea increases UDP-glucuronosyl transferase activity in rats [131] and after being absorbed, catechins are metabolized by drug metabolizing enzymes in various organs [132]. Thus, the increased glucuronidation through UDP-glucuronosyl transferase induction is postulated to contribute to the anticarcinogenic effect of green tea by facilitating the metabolism of chemical carcinogens into inactive products that are readily excreted. The interaction between 2-amino-3-methylimidazol quinoline (IQ) and green tea catechin metabolism was examined [133]. IQ is a pre-carcinogen that was originally detected in an extract of fried meat. The major route of IQ biotransformation in rats is cytochrome P-450 in the first step, followed by conjugation to a sulfate and a glucuronide conjugate. Green tea modifies IQ metabolism in rats, increasing the formation of IQ glucuronides, which are then excreted in the urine. Moreover, protection against cancers induced by polycyclic aromatic hydrocarbons by green tea catechins may be due to the inhibition of their cytochrome P-450 metabolism, but the effect of green tea on cytochrome P-450 enzymes depends on the particular form. The long-term consumption of green tea increases cytochrome P-450 1A1 and 1A2 activities, but not 2B1 and 2E1 activities, in normal rats. However, it is difficult to draw conclusions about a beneficial effect of green tea against carcinogens involving only modulation of this metabolic pathway.

12. Adverse effects of green tea

Although green tea has several beneficial effects on humanhealth, the effects of green tea and its constituents maybe beneficial up to a certain dose, yet higher doses maycause some unknown adverse effects. Harmful effects of tea overconsumption (black or green) are due to three main factors: (1) its caffeine content, (2) the presence of aluminum, and (3) the effects of tea polyphenols on iron bioavailability. Green tea should not be taken by patients suffering from heart conditions or major cardiovascular problems. Pregnant and breastfeeding women should drink no more than one or two cups per day, because caffeine can cause an increase in heart rhythm. It is also important to control the concomitant consumption of green tea and some drugs, due to caffeine's diuretic effects [134]. Some studies revealed the capacity of tea plants to accumulate high levels of aluminum. This aspect is important for patients with renal failure because aluminum can be accumulated by the body, resulting in neurological diseases; it is therefore necessary to control the intake of food with high amounts of this metal [135]. Likewise, green tea catechins may have an affinity for iron, and green tea infusions can cause a significant decrease of the iron bioavailability from the diet [136]. Moreover, theeffects of green tea catechins may not be similar in all individuals. EGCG of green tea extract is cytotoxic, and higher consumption of green tea can exert acute cytotoxicity in liver cells, a major metabolic organ in the body [137]. Another study found that higher intake of green tea might cause oxidative DNA damage of hamster pancreas and liver [138]. Yun *et al*. [139] clarified that EGCG acts as a pro-oxidant, rather than an antioxidant, in pancreatic b cells *in vivo*. Therefore, high intake of green tea may be detrimental for diabetic animals to control hyperglycemia. At a high dose (5% of diet for 13 weeks), green tea extract induced a thyroid enlargement (goiter) in normal rats [140]. This high-level treatment modified the plasma concentrations of the thyroid hormones. However, drinking even a very high dietary amount of green tea would be unlikely to cause these adverse effects in humans.

13. Conclusion

The beneficial effects of green tea are being increasingly recognize day by day, so it could be recommended that consumption of tea on regular basis. Green tea contains polyphenols, which include flavanols, flavandiols, flavonoids and phenolic acids; these compounds may account for up to 30% of the dry weight. It is the reach source of phytonutrients like flavonoids, phenolic acids, polyphenols, and catechin tannins. Green tea catechins have proved to be very versatile in providing health benefits. This means that there are potential health benefits for everyone in the consumption of green tea. Even moderate amounts of consumption (drinking 1–2 cups of tea per day) may have benefits. It is a very good thing that it is the second most popular beverage worldwide, as the differences in health in a world without green tea might be significant. Green tea also has several hydrophilic antioxidants properties as Trolox and free radical scavengers. Unlike coffee, green tea contains an amino acid L-theanine, that prevents caffeine rush and gives you the energy to sustain throughout several hours instead. Fortunately, there is a wide variety of research being performed using green tea catechins, and we are starting to see many studies performed using human subjects, as it is extremely important that we are able

to show the direct benefits to humans. Laboratory studies already showed the health effects of green tea. As the human clinical evidence is still limited, future research needs to define the actual magnitude of health benefits, establishes the safe range of tea consumption associated with these benefits, and elucidates the mechanisms of action. Development of more specific and sensitive methods with more representative models along with the development of good predictive biomarkers will give a better understanding of how green tea interacts with endogenous systems and other exogenous factors. Definitive conclusions concerning the protective effect of green tea have to come from well-designed observational epidemiological studies and intervention trials. The expansive repertoire of green tea activity in health is important, especially to those people who live in areas where medical assistance is not generally available or affordable. The development of biomarkers for green tea consumption, as well as molecular markers for its biological effects, will definitely facilitate future research in this area.

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