# Camellia sinensis

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Tea, Camellia sinensis, which belongs to the family Theaceae, is a shrub or evergreen tree up to 16 m in height. Green tea is very popular because of its marked health benefits comprising its anticancer, anti-oxidant, and antimicrobial activities, as well as its effectiveness in reducing body weight. Additionally, it was recognized by Chinese people as an effective traditional drink required for the prophylaxis against many health ailments. This is due to the complex chemical composition of green tea, which comprises different classes of chemical compounds, such as polyphenols, alkaloids, proteins, minerals, vitamins, amino acids, and others. The beneficial health effects of green tea ultimately led to its great consumption and increase its liability to be adulterated by either low-quality or non-green tea products with concomitant decrease in activity.

Keywords: biological activity ; Camellia sinensis ; phytochemistry ; quality control

## 1. Introduction

Natural products were widely employed for many centuries in home remedies, as well as in over-the-counter drug products and as raw materials for the manufacturing of various pharmaceuticals, cosmeceuticals, and nutraceuticals, both in developed as well as developing countries [1][2]. They provide a cost-effective natural solution for many ailments and possess nearly the same effectiveness as synthetic pharmaceuticals. They act via a multi-systemic effect but with relatively lower hazardous adverse effects in comparison to synthetic ones [3][4].

However, natural products are facing many challenges concerning their usage, exemplified by the difficulties related to the acquisition of sufficient pure amounts, particularly for those plants that grow in small quantities or at distant locations. Besides, a lot of problems are sparked regarding the standardization, as well as the determination, of a specific dose in a manner appropriate to the intended use. It is worthy to highlight that although natural remedies are relatively safe [5][6], the majority of lethal events reported in relation to herbal products' consumption are mainly attributable to their poor quality that eventually hindered their usage as raw materials in many pharmaceutical industries [7].

Establishing internationally recognized guidelines for assessing the quality of natural products appeared to be mandatory. Sensory, macroscopic, and microscopic examinations are the first essential steps for establishing the identity and the degree of purity of herbal materials in regard to authentic/genuine samples of the material in question. Many analytical tools are employed in quality control, including both spectroscopic and chromatographic methods [8].

Tea, *Camellia sinensis* (L.) Kuntze or *Thea sinensis* F. Theaceae, is a shrub or evergreen tree up to 16 m tall [9]. Its leaves are alternate, exstipulate, lanceolate to obovate, up to 30 cm long, 2–5 cm broad, pubescent, sometimes becoming glabrous, serrate, acute or acuminate. Fresh leaves are often picked from late March and early April to July every year [10]. Green tea represents about 20% of the dried tea which is manufactured annually and is mainly consumed in Asian countries, such as Japan, owing to its relative safety and cheaper price in comparison to other beverages [11]. This was concomitantly reflected by the annual increase in its production, which is estimated to be 6.4 percent. It is noteworthy to mention that China, India, and Sri Lanka are the biggest tea-producing countries, respectively, as reported by the 22nd Tea session held by FAO-Intergovernmental Group. Kenya and Sri Lanka constitute the two major tea-exporting countries, respectively.

## 2. Health Benefits and Biological Activities of Green Tea (*C. sinensis*)

Green tea is well-known for its marked health benefits, and, additionally, it was recognized by Chinese people as an effective traditional drink required for the prophylaxis against many health ailments [12]. Most of its crucial health benefits and biological activities are discussed below and summarized in the supplementary data Table S1.

### 2.1. Antioxidant and Hepatoprotective Activity

In traditional medicines, green tea is considered a reference drug for many plant species with respect to its anti-oxidant potency [13]. This activity is mainly attributed to its polyphenols that are represented by its flavanols, which can be readily oxidized to the corresponding *o*-quinones, and thus function as hydrogen acceptors, as well as hydrogen donors [14]. The interaction with reactive oxygen species could be accomplished by the polyphenolic compounds existing in green tea via possessing different degrees of free radical scavenging properties, particularly toward oxygen-free radicals [15] and to some extent toward nitrogen (NO) species' production inhibition [16]. The linkage of flavan-3-ol to gallic acid (GA) and the *O*-trihydroxy structure in the B ring are important criteria for the $O_2^-$ and NO scavenging activity of tea polyphenol [17]. Besides, green tea polyphenols possessing *ortho*-dihydroxyl functional groups, exemplified by epi-catechin and epi-catechin gallate, are good antioxidants that act in synergism with endogenous α-tocopherol [18].

The mechanistic potency for the anti-oxidant activity of green tea polyphenols (GTPs) was shown in different studies. GTPs act in different ways to suppress the active oxygen species generated from phenolic metabolites of benzene [19] and protect some treated oils from oxidation [20]. Other examples include increasing the excretion of carcinogenic products formed endogenously [21] and causing a marked enhancement in the salivary antioxidants in smokers, in both the short- and long term [22].

Green tea can effectively inhibit induced dose-dependent oxidative DNA damage and cell proliferation in the liver, as well as hepatotoxicity [23]. It induces the activity of some hepatic phase II enzymes, such as hepatic glutathione S-transferase (GST) [24], correcting the imbalances of the anti-oxidative system [25][26] and counteracting the induced lowered glutathione [27] in the liver. Epi-gallo catechin gallate (EGCG) and (−)-epigallocatechin-3-(3"-Omethyl) gallate are potent hepatoprotective agents, as they suppress cytotoxin-induced cell death, such as suppression of induced morphological change and induced cell death in a dose-dependent manner [28][29].

Additionally, high amounts of total phenolic compounds and caffeine prevents fat storage in the liver in high-fat diet cases [30]. Green tea is a source of highly important hexogen antioxidants that cannot be synthesized by our body and counterattack free radicals produced during metabolism of xenobiotics in the liver [31].

Moreover, green tea leaves can cause a significant reduction in elevated serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), hepatic protein carbonyls, and ROS, and thus prevent the induced liver damage [32]. Dietary green tea extract treatment reduces liver injury during nonalcoholic steatohepatitis by decreasing the pro-inflammatory signaling [33]. In addition, the extract has a substantial therapeutic effect against alcohol-induced hepatic mitochondrial DNA damage [34].

### 2.2. Anticancer and Anti-Mutagenic Activity

Green tea polyphenolics GTPs are considered to be dietary chemopreventive compounds due to their potent effect on apoptosis and cell cycle progression inhibition [35]. It acts through different mechanisms to promote the function of P-glycoprotein-mediated efflux, reducing the cellular exposure to xenobiotics [36], and through the induction of the microsomal detoxification enzyme [37]. Green tea behaves as a potent anticancer, owing to its polyphenolics, which are effective against various chemically induced carcinogens, in addition to their pronounced effect on tumor suppression [38].

Many studies showed that green tea catechins inhibit matrix metalloproteinases (MMPs), which play an important role in tumor invasion and metastasis [39]. Epi-gallo catechin gallate (EGCG) is effective against cancer [40] via the prohibition of cell cycle progression [41]. It inhibits fatty-acid synthase (FAS) [42], modulates protease activity during endothelial morphogenesis [43], and inhibits the vascular endothelial growth factor (VEGF) family [44], so it prohibits angiogenesis, which is a crucial step in the growth and metastasis of cancers [45]. Additionally, the cytotoxic activity of EGCG is also due to its auto-oxidation products, which also possess equivalent cytotoxic activities to EGCG [46]. Moreover, methylxanthines and polysaccharide inhibit tumor metastasis [47].

Green tea exerts a significant anticarcinogenic effect against many different types of cancer. Oral or topical application of green tea polyphenols possesses a considerable potential to antagonize the tumorigenic effects of some polycyclic aromatic hydrocarbons on skin [48]. Regarding photo-carcinogenesis, oral administration of green tea inhibits the formation of skin lesions produced by UVB light in a dose-dependent manner and prolongs the time of tumor appearance and decreases their number [49]. However, topical application of GTPs or EGCG protects against UVB-induced local and systemic immune suppression and skin cancer induction [50]. Also, it was found that green tea consumption reduces UVB-induced skin redness and causes significantly fewer UVA+B light-induced skin papillomas and tumors, and thus diminishes the incidence of skin cancer [51]. Moreover, many studies reported that green tea can be used in the treatment of malignant melanoma [52]. Green tea treatment was also found to decrease the induced fore-stomach, duodenal, large intestine, and colon tumors, and it can protect against the metastatic process in gastric cancer cells and strongly inhibit

the growth of hepatocellular carcinoma cells [53][54][55]. Furthermore, green tea exerted an antagonistic effect on induced micronuclei and apoptosis in colonic crypt cells [56]. Moreover, it inhibits the hyperoxidation of membrane phospholipids, which reflect the degree of DNA damage and carcinogenic alteration [57], and it causes less metachronous colorectal adenomas incidences in patients who have undergone the complete removal of colorectal adenomas [58].

Regarding lung cancer, green tea infusion revealed a notable efficacy in the alleviation of lung cancer via EGCG, which reduces the mean number of lung tumors, causes a decline in the multiplicity of lung adenomas, and counteracts metastasis with concomitant inhibition of induced lung tumorigenesis, acting synergistically with other cancer preventive agents [59][60]. Furthermore, EGCG also inhibits lung cancer stem cells [61] and stimulates apoptotic induction in human lung cancer cells [62].

Concerning leukemia, crude catechins exemplified by (+)-gallocatechin, EGC, EC, EGCG, and ECG have a suppressive effect on erythroblastic leukemia cells in a dose-dependent manner [63]. EGCG inhibits the growth of human leukemic cell lines without causing side effects and in a specific way [64]. Furthermore, EGCG exhibits antileukemic activity by inducing the differentiation of the leukemia cells, suppressing their proliferation [65] and inducing apoptosis of B-cell and T-cell chronic lymphocytic leukemia in a dose-dependent manner, without affecting healthy B-and T-cells [66]. In addition, green tea intake has a small protective effect against acute myeloid leukemia [67]. Moreover, breast cancer could be ameliorated via the daily consumption of green tea catechins. It could effectively reduce mortality triggered from induced mammary carcinogenesis, in addition to reducing the average sizes of tumors [68]. Polyphenon E, which contains about 58.4% EGCG, was noticed to exert a mild inhibitory effect on the early promotion stage [69]; however, catechins may act in the post-initiation stage, but not in a dose-dependent manner, in addition to reducing recurrences [70][71]. Recently, it was found that green tea drinkers have no excess risk for epithelial ovarian cancer [72]. Furthermore, green tea has proved to have antiproliferative effects against human prostate cancer cells [73] and can lead to cell growth inhibition in some prostate cancer cells [74] showing potent inhibition of 5α-reductase enzyme, which may be involved in the development of benign prostatic hyperplasia, hirsutism, and prostate cancer [75][76]. GTPs also strongly inhibit the growth of renal cell carcinoma cell lines in a concentration-dependent manner [77]. It is worthy to highlight that green tea catechins possessing the gallate group act as anticancer agents on glioblastoma cells and can prevent the inflammatory processes associated with aggressive glioma tumor growth [78][79]. Nowadays, green tea serves as a diet-derived immune-modulatory chemopreventive agent; as many of its contained flavonoids stimulate natural killer (NK) cell activity, so it may be used in the treatment and prevention of malignant diseases [80].

Meanwhile, aqueous extract of green tea has a marked antimutagenic activity against different major classes of dietary and occupational carcinogens [81]. This activity may be attributed to different mechanisms, such as improving the fidelity of DNA replication [82], affecting carcinogen metabolism [83], direct interaction between the reactive genotoxic species of the various promutagens, and nucleophilic tea components. In addition, it causes a potent inhibition of the cytochrome P450-dependent bioactivation of the promutagens [84], acting intracellularly as a blocking or suppressive agent [85], and potent dose-dependent antigenotoxic activity [86]. Besides the antimutagenic activity of green tea, it has anticlastogenic effects [87].

### 2.3. Antimicrobial and Antiviral Activity

Many studies reported the antimicrobial activity of green tea. Green tea is effective against *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Vibrio cholerae O1*, owing to the bactericidal catechins that primarily cause defection in the bacterial membranes [88]. Green tea is also effective against various bacteria that cause dental caries, such as *Escherichia coli*, *Streptococcus salivarius,* and *Streptococcus mutans* [89]. EGCG and gallocatechin gallate (GCG) markedly inhibit the secretion of extracellular Vero toxins from enterohemorrhagic *Escherichia coli* cells into the culture supernatant fluid [90]. Raw extract of green tea, especially gallocatechin gallate (GCG), is able to suppress 1-deoxy-d-xylulose 5-phosphate reductoisomerase activity, which is an antimicrobial target [91]. Furthermore, it can also reduce the lethality of ricin toxin [92], but it has a poor activity against *Babesia divergens* that infect cattle [93].

EGCG can inhibit the activity of *Salmonella typhimurium* type III, and thus reduce the bacterial invasion into host cells [94]. Green tea extract is bactericidal against Gram positive bacteria and bacteriostatic against Gram negative ones, with less antifungal activity against *Aspergillus niger* and *Penicillium chrysogenum* [95].

In addition, tea polyphenols have the ability to inhibit the development and growth of bacterial spores, as in case of *Bacillus stearothermophilus* and *Clostridium thermoaceticum*, due to their ability to decrease the heat resistance of these bacterial spores when added at high temperature [96]. However, chlorogenic acid induces the apoptotic markers through excessive potassium efflux and an apoptotic volume reduction, which induces cytosolic calcium uptake and cell cycle arrest in *Candida albicans*, in addition to its ability to induce caspase activation and DNA fragmentation [97].

Tea exhibits antiviral activity against human viruses and serves as a diet-derived immune-modulatory chemopreventive agent, as many of its contained flavonoids stimulate NK cell activity, so it may be used in the treatment and prevention of viral diseases [80]. Recently, it was found that EGCG is capable of inhibiting the Brazilian strain of Zika virus entry [98]. Additionally, topical application of EGCG can be used to prevent the sexual transmission of HIV, as it disaggregates existing amyloid fibrils termed semen-derived enhancers of viral infection fibers and inhibits the formation of new ones [99].

### 2.4. Anti-Schisosomiasis and Antiparasitic Activity

Green tea could be able to protect liver cells in mice after being infected with *Schistosoma mansoni*, and thus decreases cellular necrosis and regenerates total protein and glycogen levels partially. This could be achieved through suppression of the oxidative stress, owing to its scavenging properties toward free radicles [100]. Moreover, green tea has an antiparasitic activity as it noncompetitively inhibits the activity of *Toxocara canis* [101].

### 2.5. Cardioprotective Activity

Green tea could improve the risk factors for heart disease [102], as it significantly reduces total cholesterol, low density lipoprotein (LDL) cholesterol, and blood pressure [103]. It also improves microvascular function and skin oxygen tension in both older and younger populations [104]. Nonfermented Chinese green tea is considered to be an ideal beverage to prevent the incidence of coronary heart disease. Its consumption, together with its catechin-rich fractions, lowers the risk of coronary heart diseases through delaying atherogenesis by significantly preventing endothelial cell induced LDL oxidation and foam cell formation [105]. The inhibition of advanced glycation end products formation in collagen represents another important mechanism for the protective effects of green tea catechins against cardiovascular diseases [106].

The consumption of green tea decreases the risk of myocardial infarction (MI) in a dose-dependent manner up to ≥4 cups/day [107], as it reduces cardiac hypertrophy, improves systolic and diastolic dysfunction, restores the antioxidant enzyme activity, and stimulates the glucose pathway and mitochondrial function with reduced apoptosis after MI [108]. High dietary intake of green tea may be useful in the reduction and prevention of cardiac injury following ischemia [109].

The flavonoids that exist in green tea perform its cardio-protective effect by improving the reserve in coronary flow velocity [110]. EGCG is able to reduce both arsenic- and doxorubicin-induced cardiotoxicity [111]. It reduces the inflammation and preserves the cardiac function, with lowered mortality rate [112]. Concerning EC, it may be involved in treating cardiac arrhythmia [113]. Meanwhile, EC supplementation has a cardioprotective effect without changing blood pressure, arterial stiffness, or the blood lipid profile [114].

Additionally, green tea can be used as anti-hypercholesterolemic agent by acting in several ways, such as enhancing hepatic excretion of cholesterol or inhibiting absorption of cholesterol in the alimentary tract [115]. This is accompanied by increasing fecal bile acids and cholesterol excretion, resulting in the lowering of the plasma cholesterol [116] and the lowering of LDL oxidation by increasing cellular antioxidant status or inhibiting oxidizing enzyme activities in the arterial wall [117]. Other possible mechanisms include diminishing the levels of α-ketoglutarate and pyruvate dehydrogenases enzymes, which are vital in the cholesterol biosynthesis [118] or inhibition of the rate limiting enzyme of cholesterol biogenesis, squalene epoxidase (SE) [119]. Green tea also causes a prolongation in LDL oxidation lag time by flavonoids [120], inhibition of serum triglyceride elevation [121], and prevention of fat storage in the liver, lowering blood lipids and increasing fecal excretion of triglycerides [30].

Fresh green tea fermented under nitrogen gas produces γ-aminobutyric acid (GABA)-rich tea, which was proved to prevent the occurrence of hypertension [122]. Theanine exerted a significant decline in blood pressure following a dose-dependent manner [123]. EGCG and EGC were found to inhibit dopa decarboxylase enzymes in a concentration- and time-dependent manner, which is a known target for drugs used in hypertension [124]. EGCG that was chronically infused in the hypothalamic paraventricular nucleus (PVN) attenuates hypertension by chronic inhibition of ROS, in addition to regulating the balance of neurotransmitters, as well as cytokines, in the PVN [125]. Green tea extract was found to prevent high angiotensin II dose-induced hypertension and the accompanied organ damage by preventing or scavenging superoxide anion generation [126]. Decaffeinated green tea extract also reduces the metabolic syndrome through reduction of the formation of ROS, which results in lowered blood pressure [127].

Regarding green tea anti-thrombotic activity, it was found that unprocessed tea extracts can significantly reduce the levels of thromboxane-B2 and then eliminate the aggregation of platelets to produce microthrombi, while processed ones are unable to form any inhibition, significantly owing to the presence of a heat-labile compound [118]. Possibly, green tea has a fibrinolytic effect [102]. In addition, the catechins inhibit induced platelet aggregation in vitro in a dose-dependent manner, without changing the coagulation parameters [128]. The tea can also be used to prevent red blood cell hemolysis [129].

Different green tea extracts have different degrees of inhibition of dehydration of stored sickle cells, and this inhibitory activity increases by increasing the number of hydroxyl groups [130].

### 2.6. Antidiabetic and Anti-Obesity Activity

Green tea is used for the amelioration of diabetes and its complications, acting as a renoprotective in diabetes mellitus, in addition to the ability of EGCG to inhibit angiogenesis that is involved in many diseases, such as diabetic retinopathy [45][131]. Furthermore, EGCG can help in controlling hyperglycemia and alleviating diabetes complications via reducing plasma glucose, insulin level, and liver and kidney weight [132]. Recently, it was found that EGCG is useful for resensitizing insulin-resistant muscle [133].

The administration of GTPs significantly increases glucose tolerance and reduces induced elevated serum glucose levels [134]. Floratheasaponins A, B, and C in the flower buds of green tea exhibit potent inhibitory effects against sucrose-induced serum glucose elevation [135]. Green tea water-soluble polysaccharide fraction has an inhibitory effect against α-amylase, which leads to decreased blood glucose levels [136], along with galloyl moiety in catechin, which increases the inhibition of pancreatic α-amylase, due to enhanced association with the enzyme active site [137].

Regarding obesity, green tea extract is a well-tolerated natural product for the management of obesity by reducing fat digestion through marked inhibition of digestive lipases, such as gastric and pancreatic lipases, especially by saponins, which lead to altered lipid emulsification in gastric or duodenal media [138]. In addition, it stimulates thermogenesis/energy expenditure and fat oxidation mainly by EGCG and caffeine [139], without significant differences in either plasma cholesterol or blood pressure [140]. Furthermore, chronic usage of short-time decoction of green tea decreases perirenal and epididymal adipose tissues and weight gains in high-fat diet cases [30].

Recent studies confirm that a mixture of green tea catechins and caffeine has a beneficial effect on body-weight management through sustained energy expenditure, fat oxidation, and preservation of fat-free body mass [141]. Polyphenols such as EGCG can increase lipolysis, in addition to possessing anti-adipogenic effects through being a fatty-acid synthase (FAS), which is a possible therapeutic target for appetite and weight control [142][143]. Polyphenols have “exercise mimetic” properties through exercise-inducible pathways [139].

### 2.7. Gastrointestinal Tract Problems Relieving Activity

The purified green tea EC can cause both endothelium-dependent and -independent mesenteric arteries relaxation [144]. However, EGCG preserves the aortic thickness and regenerates elastin content, due to its anti-inflammatory effect, so could prevent abdominal aortic aneurysm [145]. Furthermore, high green tea consumption is associated with a reduction in the risk of precancerous chronic atrophic gastritis [146].

In addition, floratheasaponins A, B, and C in flower buds exhibit potent inhibitory effects against ethanol- and indomethacin-induced gastric mucosal lesions, so green tea seems to have a gastro-protective effect [135]. However, daily intake of green tea is able to alter the growth and composition of the intestinal flora and modulate the genesis of potentially harmful agents like *Clostridium difficile* and *Clostridium perfringens*, due to the effect of its components, such as vitamin C and polyphenols [147]. Green tea has recently proved to modulate the fecal microbiome and thus endogenous metabolites [148].

### 2.8. Neuroprotective Activity

Green tea extract has a protective effect on the ischemia/reperfusion-induced brain injury and behavior deficit. It also reduces the number of ischemia/reperfusion-induced apoptotic neuronal cells [149]. GTPs, EGCG, ECG, EGC, and EC are able to protect synaptosomes from induced lipid peroxidation damage [150]. EGCG alone has a protective effect against stress-induced neural injuries [151]. EGCG was shown to be easily absorbed from the digestive tract and penetrate the brain, reaching levels similar to those found in lung, liver, kidney, and others [152]. It has a neuroprotective effect against neuronal damage following transient global ischemia in the gerbils acting by different mechanisms as angiogenesis in the early stage of ischemic stroke promoting [153][154]. Regarding neurotoxicity, l-theanine has a protective effect against cadmium-induced neurotoxicity by reducing brain cadmium levels and oxidative damage, which lead to neurodegenerative diseases [155].

In addition, GTPs can be considered therapeutic agents to alter brain aging processes by serving as neuroprotective agents in major neurodegenerative disorders, such as Parkinson’s disease and Alzheimer’s disease [156][157]. In addition, green tea catechin intake may be useful in the improvement of the morphologic and functional changes that occur naturally in the accelerated senile brains [158]. EGCG and EGC were found to be inhibitors of dopa decarboxylase enzyme

in a concentration- and time-dependent manner [124]. Green tea containing high levels of EGCG prevents the loss of tyrosine hydroxylase (TH)-positive cells in the substantia nigra [159]. Both tea and EGCG, when used alone or with Parkinson's disease's inducers, can decrease the neuronal nitric oxide synthase (nNOS) expressions in the substantia nigra, which provides a neuroprotective effect [160].

Regarding Alzheimer's disease, EGCG may be beneficial for its prevention, as it has protective effects against amyloid ß-induced hippocampal neuronal apoptosis [161] in which neuronal loss is accompanied by the deposition of amyloid ß protein in senile plaques [162]. EGCG regulates the growth and survival of astrocytes without being cytotoxic. Green tea catechins possess an inhibitory effect against *β*-secretase, which is known as one of the most important amyloid precursor protein cleaving enzymes in Alzheimer's disease [163]. EC reduces amyloid-β-induced *β*-secretase-1 expression and thus inhibits the most toxic amyloid-β aggregates [164].

The theanine existing in green tea enhances the memory and learning ability, owing to its significant effect on the release or reduction of memory- and learning-linked neurotransmitters, such as dopamine and serotonin [123][165]. Polyphenols also have a potential role in the prevention/treatment of dementia [166]. It was proved that combined ingestion of EGC and GA increases the learning ability in a better way than EGCG, which reaches the brain parenchyma at a very low concentration [167]. Additionally, theanine may affect emotions by interacting with neurotransmitters in the brain, due to a modulation of synaptic transmission [38]. Moreover, drinking theanine-rich and low-caffeine green tea has anti-stress effects, as theanine, EGC, and arginine together can counteract the effect of caffeine and EGCG on psychosocial stress-induced adrenal hypertrophy [168]. Theanine also produces a marked relaxation effect due to its rapid absorption and transportation to the brain in 30 min, without suffering any metabolic degradation [123].

### 2.9. Anti-Inflammatory, Analgesic, Antipyretic, and Anti-Allergic Activity

Green tea is considered to be a potent anti-inflammatory and antipyretic agent [169][170]. EGCG reduces nitric oxide production via its gallate structure [171]. It inhibits the endothelial cell growth which leads to the inhibition of angiogenesis that is involved in many diseases, such as chronic inflammation [45]. The non-polyphenolic fraction of green tea represented by Pheophytin a and b exerts suppressive activities against the activation of human polymorphonuclear neutrophils (PMNs) associated with inflammatory reactions in a dose-dependent manner [172]. Moreover, green tea extract/tablets showed a high efficacy in controlling pain, particularly in patients suffering from osteoarthritis as well as [173].

Regarding the anti-allergic activity of green tea, polyphenols are considered to be the major inhibitory components of hot-water-soluble extracts of green tea against histamine release from mast cells [174]. In addition, green tea has an anti-allergic effect due to leaf saponins [175] and floratheasaponins from flower buds that possess anti-allergic activities, as well [176]. It was reported that methylated EGCG blocks the production of two compounds in the body mainly involved in producing an allergic response, histamine and immunoglobulin E (IgE), and works by triggering and sustaining allergic reactions. It is worthy to mention that green tea can activate heat-generating mechanisms in the body such that a fall in core body temperature can be lowered upon cold exposure [177].

### 2.10. Skeletomuscular System Relieving Activity

EGCG has direct vasodilator action in skeletal muscle and increasing muscle microvascular blood flow [178]. It can induce myogenic differentiation [179] and increase the recovery of muscle mass and function [180]. Moreover, EGCG induces apoptotic cell death of osteoclasts in a dose-dependent manner with no effect on osteoblasts [181]. Appropriate concentrations of EGCG have an anti-inflammatory effect in the treatment of collagen membranes and thus can be used in bone regeneration [182]. It was also found that green tea has a protective effect against induced bone and hyaline cartilage alteration [183]. Furthermore, EGCG enhances osteoprotegerin synthesis, which is secreted from osteoblasts, and suppresses osteoclastic bone resorption, especially in the elderly [184]. Meanwhile, EGCG has the potential to inhibit the development of arthritis, as pretreatment with EGCG inhibits the release of induced lactate dehydrogenase in human chondrocytes of osteoarthritis cartilage [185]. Green tea extract can also be used as an adjunctive treatment, because it can control the pain and improve the knee-joint physical function in adults with osteoarthritis [186].

Green tea can be useful as a medicament for treatment of infected root canals, as Japanese green tea extracts have antibacterial and bactericidal effects against some facultative anaerobes and obligative anaerobes [187]. It also has a high amount of fluoride, which may help strengthen teeth and bones and reduce tooth decay [188]. Besides fluoride, green tea has a high concentration of polysaccharides, such as pectin, which enhances the inhibition activity against *Streptococcus mutans*, thus preventing dental caries [189]. Green tea is also effective against other various bacteria that cause dental caries, such as *Escherichia coli* and *Streptococcus salivarius* [89]. The combination of green tea and miswak (*Salvadora*

*persica* L.) extracts exhibits synergistic antiplaque properties [190]. Additionally, green tea can be used to prevent periodontal diseases, due to its matrix metalloproteinases (MMPs) inhibitory activity in a dose-dependent manner [191], with particular reduction in their secretion in gingival fibroblasts [192].

### 2.11. Miscellaneous Activity

Moreover, green tea experienced a lot of pronounced activities in relieving skin damage and promoting wound healing. Oral or topical treatment of GTPs prevents damages such as ultraviolet (UV)-induced sunburn response, immuno-suppression, and photo-aging [193], such as dermal extracellular damage [194] and DNA damage [195]. Treating the skin with green tea extracts inhibits induced erythema response in a dose-dependent manner, especially when treated with EGCG and ECG [196], due to the ability of EGCG to inhibit UVB-induced oxidative stress [197]. In addition, green tea ethanol extract is effective in the healing process of surgical wounds, as it decreases the healing duration [198]. Recently, it was found that tannase-converted green tea extract can be used in cosmetics as a skin anti-wrinkling or depigmenting agent [199], as tannase-derived bioconversion, which occurs on catechins compositions in green tea, was found to be useful in improving the antioxidant and radicals scavenging activities [200].

It is notable that anti-amyloidogenic activity has been attributed to oxidized EGCG comparable to the intact molecule, as it has a disruptive effect on preformed fibrils more than the native form [201]. Green tea revealed a high potency in the prohibition of proMMP-9 and MMP-9 activities, which play an important role in the development of pulmonary hypertension [202]; meanwhile, l-theanine proved efficacy in the alleviation of oxidative stress-induced airway inflammation in asthma [203]. Recent studies showed that dietary supplementation enriched with green tea promotes the antioxidant defense system in plasma and thus provides protection against oxidative damage induced by both short-term muscular endurance test and long-term strength training [204]. Additionally, the tea extract can prolong the time to exhaustion [205] and improve vascular function and physical performance in healthy individuals [206].

Green tea extract has a protective effect against induced reproductive toxicities and reduced testicular androgen receptors [207]. In addition, green tea improves induced damage of the reproductive system; this is probably due to its high catechins content [208], as catechins have a quenching effect on the reactive oxygen species that lead to oxidative stress in male and female reproduction systems and cause infertility [209]. EGCG increases the total efficiency of fertilization through improving the in vitro penetration rate of the sperms [210]. Meanwhile, oral administration of polyphenone-60 (P-60), green tea extract catechins, can stimulate goiter and reduce weights of the body, testis, and prostate gland, along with elevation in plasma thyroid stimulating hormone (TSH), luteinizing hormone (LH), and testosterone levels and reduction in tri-iodothyronine (T3) and thyroxine (T4). P-60, as a whole, and some of its constituents, can inhibit human placental aromatase activity which then can be used as preventive agents against benign prostatic hypertrophy (BPH) [211].

Regarding the effect of green tea extract on eyes, it has potential cataracto-static ability and can delay the progression of lens opacity, as it decreases smoking-induced frequencies of micronuclei in peripheral-blood lymphocytes [212]. It also counteracts the oxidative insult caused by cigarette smoke that causes oxidative damage to the constituent molecules and consequent lenticular opacity [213]. GTPs can bind to the cleft between the domains of human γB-crystallin protein, which is then protected from UV induced-oxidative stress [214].

Green tea may have selective protective effects within the body, especially on the kidney [215]. Green tea tannins, especially EGCG and ECG, cause a dose-dependent decrease in the progression of renal failure [216]. Recently, it was found that green tea extract can prevent the induced lipid peroxidation and antioxidant depletion in the kidney [217].

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