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Review

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Recent Advances in the Understanding of the Health Benefits and Molecular Mechanisms Associated with Green Tea Polyphenols

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ABSTRACT: Tea, leaf, or bud from the plant *Camellia sinensis*, make up some of the beverages popularly consumed in different parts of the world as green tea, oolong tea, or black tea. More particularly, as a nonfermented tea, green tea has gained more renown because of the significant health benefits assigned to its rich content in polyphenols. As a main constituent, green tea polyphenols were documented for their antioxidant, anti-inflammation, anticancer, anticardiovascular, antimicrobial, antihyperglycemic, and antiobesity properties. Recent reports demonstrate that green tea may exert a positive effect on the reduction of medical chronic conditions such as cardiovascular disease, cancer, Alzheimer's disease, Parkinson's disease, and diabetes. The health benefits of green teas, in particular EGCG, are widely investigated, and these effects are known to be primarily associated with the structure and compositions of its polyphenols. This Review focuses on the diverse constituents of green tea polyphenols and their molecular mechanisms from the perspective of their potential therapeutic function. Recent advances of green tea polyphenols on their bioavailability, bioaccessibility, and microbiota were also summarized in this article. Dietary supplementation with green tea represents an attractive alternative toward promoting human health.

KEYWORDS: *green tea, polyphenols, EGCG, functional effect, molecular mechanism*

INTRODUCTION

After water, tea is the most consumed beverage around the world. Originating from China, tea has a long history that spans across numerous countries over thousands of years.[1,2] From ancient times to the present, tea has always been regarded as the traditional Chinese medicine capable of ameliorating or preventing all sorts of disorders.[1] Today, more than 30 countries around the world are producing different varieties of tea, not only as a relaxation drink but also for the its documented health benefits supported by a myriad of scientific studies.[2]

On the basis of their respective manufacturing processes, teas are categorized into nonfermented green tea, semi-fermented oolong tea, and fermented black tea. In the case of green teas, the initial stages of manufacturing involve steaming or roasting, which will inactivate the activity of polyphenol oxidase hence preventing any oxidation from occurring during subsequent processing steps. As such, green tea preserves the native structure of its polyphenolic compounds as well as its overall compositions. In green tea, polyphenols in green tea is a general designation for catechins, flavones, anthocyanins, and phenolic acids; besides, there are also some other minor polyphenols that also exist such as epigallocatechin gallate, flavonol glycoside, and tannins. In green tea, the polyphenol compounds are the main constituents accounting for 24−36% in dry weight, followed by its protein content (15%), lignin (7%), amino acids (3−4%), caffeine (2−4%), organic acid (2%), and chlorophyll (0.5%).[3] Catechins represent the majority of the polyphenols present in green tea: (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG) and (−)-epigallocatechin-3-gallate (EGCG) are the 4 most abundant catechins. In vitro studies have shown that green tea polyphenols (GTP) are potent free-radical scavengers and antioxidants, and these effects were attributed to their phenolic hydroxyl groups. Given the contribution of oxidative stress to the onset and progression of chronic pathological conditions, the antioxidative activity found in green tea was documented to prevent a variety of diseases. Moreover, EGCG was also described as a second signal messenger, a stimulator of plasma membrane proteins, and a modulator of metabolic enzymes, and it was also reported to be involved in cell signaling and transcription pathways.

A number of animal and clinical studies have documented the preventive effects of GTP on cardiovascular disease, cancer, obesity, diabetes, and allergic disease and most of the in vivo study is based on the previous mechanism of polyphenols healthcare properties and then give further illustration on the molecular signal pathway. While a myriad of studies has been published, the exact mechanistic pathways underlying the biological activities of green tea polyphenols remains obscure. In addition, the bioaccessibility and bioavailability of polyphenols are an inescapable barrier for the intake of green tea in normal daily life. In this Review, we sought to report on the most recent studies investigating the chemical structures, signaling and molecular pathways associated with GTP, for a

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better understanding of the biological activity and health benefits of green teas.

CHEMICAL STRUCTURE

When referring to polyphenols in green tea, catechins first come to mind as they account for 60−80% in all polyphenols present in green tea. As mentioned above, the major catechins are (−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC) as shown in Figure 1. EGCG is the most

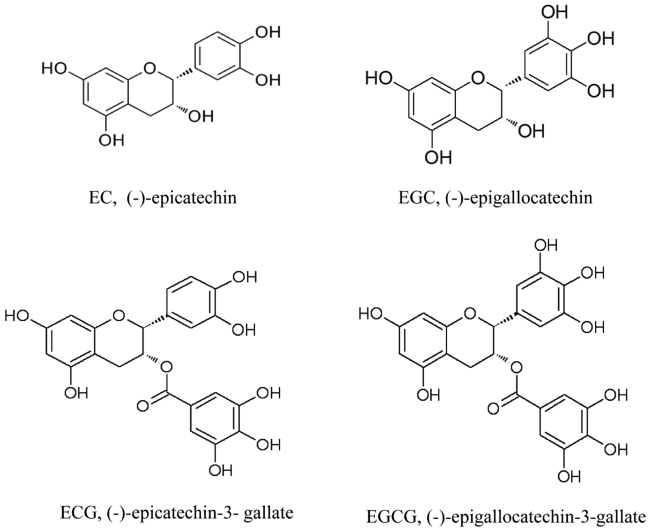

Figure 1. Chemical structures of major catechins in green tea.

abundant catechin found in green tea, which accounts for 30−50% of all catechins in a typical cup of brewed green tea (1 g of leaves steeped for 3 min in 100 mL of water) and is also believed to have the most potent pharmacological activity.[4,5] Moreover, some phenol derivatives can also be found in green teas, such as quercetin, myricetin, kaempferol, along with their respective glycosides characterized by a 4-oxo 3-hydroxy C ring. The chemical structure of polyphenols is characterized by the presence of several hydroxyl groups on different sites of a carbon atom, which may interact with reactive oxidizing species hence inhibiting oxidative stress. As such, the antioxidant activity of green tea is tightly associated with the electron-rich properties of polyphenols. The 2,3-double bond and the unsaturated 4-oxo group in the C-ring facilitates electron delocalization of o-dihydroxyl catechol within the B-ring.[6] In particular, the provision of hydrogen bonds to the 4-oxo group in the C-ring of catechins is another structural feature contributing to the antioxidant activity of GTP.

BIOLOGICAL ACTIVITIES

Antioxidant Activity. The biological activities of polyphenols, in particular EGCG, are well-known and their antioxidant properties have been widely documented. The antioxidant effect of GTP and associated potential mechanisms were summarized in Table 1. In a study by Shah et al.,[7] green tea extract (GTE) was shown to be more effective than black tea extract likely due to the higher content in polyphenolic compounds found in green teas. In vitro, green tea EGCG was reported to reduce reactive oxygen species (ROS) levels, increase cell viability, and inhibit H_2O_2-induced cell apoptosis, which was mainly regulated via phosphorylation of Akt and JNK pathways.[8−10]

Similarly, studies have described the protective effects of EGCG on the viability of lead-exposed cells and on the synaptic plasticity of Wistar rats exposed to lead.[11] Bleomycin (BLM) is a chemotherapeutic agent that breaks the strands of DNA in the presence of iron and oxygen and promotes ROS formation.[12] The protective impact of EGCG on BLM-induced oxidative stress and pulmonary fibrosis was demonstrated in Wistar rats, where collagen deposition and wet−dry lung weight ratio were significantly reduced and was accompanied by a restoration of GST, NADPH, and quinone oxidoreductase 1 (NQO1) levels.[13] The activity of antioxidative enzymes such as superoxide dismutase (SOD), catalase (CAT), and

Table 1. Antioxidant Activity of Green Tea and Its Polyphenols

in vitro	in vivo	compound	observed effects	reference
human colon cancer cell line (Colo-205)		GTP	↓ lipid peroxidation	8
			radical scavenging capacity	
			antiproliferative activity	
pancreatic TC1-6 cells		EGCG	↑Akt activation; ↓ p38, caspase 3 and JNK pathway; ↓ ROS level; ↑ cell viability	10
			↓ apoptosis	
bladder cancer cells		EGCG	↑ cell viability	11
	Wistar rats	EGCG	↓ ROS; ↑ cell viability; free radical scavenger; restored mitochondrial function, protected rats from synaptic plasticity deficits	12
	Wistar rats	EGCG	↓ collagen deposition; ↓ severity of fibrosis	14
			↑ activities of SOD, CAT, GPx; ↑ Nrf2 expression; restored vitamin C, E, A levels	
breast epithelial MCF10A cells		EGCG	↑ Akt phosphorylation and antioxidant enzymes; ↑ Nrf2 expression	19
	male Kunming mice	EGCG	↑ Nrf2 expression; ↑ heme oxygenase 1, NAD(P)H, quinone oxidoreductase 1 , glutathione S-transferase (GST)	20
	mice	EGCG with polyunsaturated fatty acids	↑ metal chelator capacity; ↑ peroxyl radical scavenging activity	28
	Japanese Quails	EGCG	↑ Nrf2 expression and antioxidant enzymes	47

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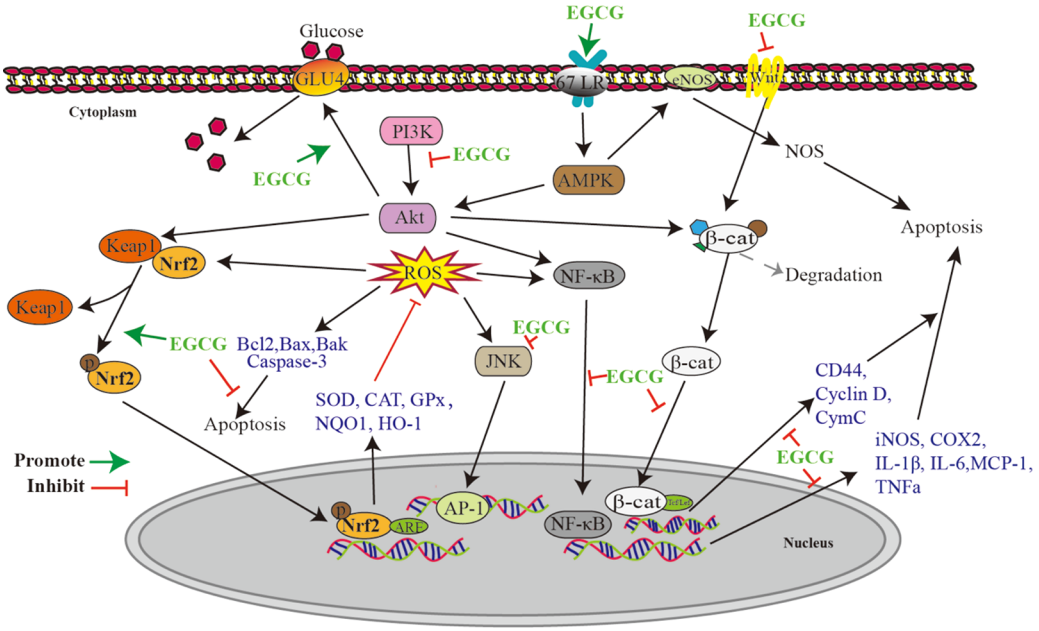

Figure 2. Schematic diagram illustrating the mechanism by which green tea EGCG associated with the regulation on PI3K/Akt, Nrf-2/Keap1, AMPK, and Wnt/β-catenin cell signaling pathways.

glutathione peroxidase (GPx) was also upturned to near normal values upon administration of EGCG to BLM-treated rats, indicating that EGCG treatment might provide resistance to oxidative stress by modulating enzymatic activity.[14] Similar results were reported by Ahmed et al.,[15] where the administration of EGCG was shown to decrease electromagnetic radiation-induced oxidative stress in the hippocampus and striatum of rats through modulation of antioxidative enzymatic activity. In the antioxidant cell signaling pathway, NF-E2- related factor 2 (Nrf2), a master regulator of antioxidant enzymes and detoxification genes, was shown to interact with Kelch-like ECH-associated protein 1 (Keap1) to reduce oxidative stress and improve overall the antioxidative functions of organisms.[16,17] In vitro, stimulation of epithelial MCF10A cells with EGCG was shown to promote the activity of antioxidative enzymes and promote the release of Nrf2 for nuclear translocation, hence promoting antioxidative functions and survival under conditions of oxidative stress.[18] In a study by Sriram et al.,[13] EGCG was shown to protect mouse lung from pulmonary fibrosis as evidenced by an increased expression of Nrf2 and by restoration of antioxidant enzymatic activity through the activation of Nrf2-Keap1 signaling. Heme oxygenase 1 (HO1), NADPH, NQO1, and glutathione S-transferase (GST) are downstream target genes of the Nrf2-Keap1 signaling pathway, which were found to be up-regulated upon administration of GTP or EGCG.[13,19] Generally speaking, activation of the Nrf2-Keap1 signaling pathway plays a major role on the antioxidant effect of GTP as shown in Figure 2. In comparison with different derivatives of EGCG, ECG, EGC, and EC, the permethylated derivatives showed no antioxidant effect, and the methylated derivatives only showed very weak antioxidant effect.[20] The ester derivatives with stearic acid, docosahexaenoic acid, and eicosapentaenoic acid have enhanced lipophilicity and better antioxidant effect compared with EGCG itself.[21] Thus, the structure of polyphenols is fully considered when constructing the derivatives of it, which would then promote the functional activities.

Anticancer Activity. Observations originating from epidemiological and laboratory studies, have determined that GTP and EGCG are potent anticarcinogenic and chemopreventive agents. In vitro and in vivo studies have determined that GTP was involved in cell apoptosis, cell proliferation, cell cycle in tumor growth and cell migration, all resulting in reduced risks for some certain cancer types, including breast, prostate, colorectal, and skin cancers, as represented in Table 2.

In the early stages of carcinogenesis, lipid-peroxidation-induced DNA mutagenesis is generally increased through the accumulation of malonaldehyde (MDA), which may in turn promote the risk of developing cancer.[22] The levels of malondialdehyde-DNA adduct 3-(2-deoxy-β-D-erythro-pentofuranosyl) pyrimido [1,2-α] purin-10 (3*H*)-one (M_1dG) were shown to be much higher in breast cancer patients compared with healthy individuals. Treatment with GTP was shown to reduce M_1dG levels in human-derived breast carcinoma cells in a dose-dependent manner.[22] M_1dG adduct levels, as well as the volume and size of tumors in TAg mice, were also shown to significantly decrease upon administration of GTP, resulting in a slight life prolongation in mice.[23] In breast cancer cell line MCF-7, EGCG (10−50 μg/mL) was found to exert a dose-dependent activation of caspase-9 and inhibition of the expression of survivin, a major member of the apoptosis inhibitor gene family, which is involved in the Akt signaling pathway.[24] In a double-blind, placebo-controlled study, a one-year treatment with GTP (600 mg/day) was conducted on 60 male volunteers with high-grade prostate intraepithelial neoplasia and led to a 90% chemoprevention efficacy without any adverse effects.[25] An 11-year follow up cohort study involving 49 920 Japanese men, who consumed green tea as a habit, showed a dose-dependent reduction in their risks of developing advanced prostate cancer.[25] GTPs were also investigated for their antiproliferative effects in human colorectal cancer cells: EGCG was shown to be the most potent at inducing cell apoptosis in both early and late stages and at arresting cell cycle leading to the targeted death of

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Table 2. Anticancer Activity of Green Tea and Its Polyphenols

in vitro	in vivo	compound	observed effects	reference
human-derived breast carcinoma cells MDAMB-468	mammary adenocarcinoma mice	GTC	↓ malondialdehyde-DNA adduct M1dG	22
human breast cancer cell		EGCG	↓ AKT signaling ↑ Caspase-9	23
human breast cancer		GTP, EGCG	↓ proliferation	24
MDA-MB-231 cell			↑ apoptosis	
	male volunteers	green tea	↓ prostate cancer development	25
human colorectal cancer cell lines HCT-116 and SW-480		EGCG, EC, EGC, ECG, C, GCG, CG, GC, GA, CA	↓ proliferation	26
			↑ apoptosis	
	colon cancer rat	GTP	↑ apoptosis	27
			↓ β-catenin signaling	
			↓ D1. Retinoid X receptor (RXR)α	
	male mice	EGCG-DHA, perbutyrated EGCG	↓ aberrant crypt foci (ACF) number and size	28
			↓ iNOS and COX-2	
	ApcMin/+ mice	EGCG; ECG	↓ cell proliferation, ↓ β-catenin nuclear expression, and phospho-Akt levels	29
			↑ caspase-3	
human breast cancer cell line MCF-7		EGCG	↓ phosphatidyl-inositol-3-kinase (PI-3K)	31
lung metastasis of B16 melanoma cells		EGCG	↑ cell stiffness	32
			↓ cell migration	
human lung cancer cell line PC-9		ECCG	↓ tumor volume	33
			↓ self-renewal of cancer stem cells	
AI PC-3 human prostate cancer bone metastasis cell line			↑ apoptosis	35
			↓ PI3K/Akt	
			↓ multidrug resistance-related protein	
colorectal cancer cells	male athymic nude mice	EGCG	↓ Notch1, Bmi1, Suz12, and Ezh2	36
			↓ tumor growth	
squamous carcinoma HNSC stem cells		EGCG	↓ sphere forming capacity	37
			↑ Oct4, Sox2, Nanog, and CD44	
			↓ Notch signaling	
human NPC cell lines		EGCG	↓ NF-κB p65 activity	38
			↓ cell migration	
	preclinical mouse models	EGCG	↑Bax	118
			↑ caspases	
			↓ Ki-67 and PCNA	

cancer cells.[26] Xiao et al.,[27] observed the development of aberrant crypt foci (ACF) in the azoxymethane (AOM)-induced colon cancer rat model. The same authors also showed that treatment with Polyphenon E (PPE, a standardized green tea preparation containing 65% EGCG) led to a decrease in the total number of ACF and aberrant crypts, along with a dose-dependent reduction in the percentage of large ACF (four or more crypts) and ACF with high- grade dysplasia. PPE was also reported to maintain the expression of retinoid X receptor (RXR)-α hence preventing carcinogenesis. Zhong et al.,[28] did not use PPE, but rather focused on the effects of an EGCG-DHA mixture (containing 42.2% EGCG) on colon carcinogenesis in AOM-treated mice by monitoring ACF formation and expression of two tumor-promoting enzymes, i.e., nitric oxide synthase (iNOS) and cyclo-oxygenase-2(COX-2). EGCG-DHA was shown to reduce the number and size of ACFs, especially against large ACF formation (100% inhibition), suggesting that the combination of fatty acid and EGCG might have had a synergistic anticarcinogenic effect.[28] Moreover, the expression of iNOS and COX-2 were significantly down-regulated by EGCG-DHA in a dose-dependent manner. In a study by Hao et al.,[29] the oral administration of EGCG led to inhibition of cell proliferation, apoptosis, and decreased levels of β-catenin through inhibition on Akt cell signaling pathway, along with upregulated expression levels of cleaved caspase-3 and RXRα expression. Matrix metalloproteinase-2 (MMP-2) plays a key role in tumor cell migration, and it is a very sensitive indicator of cancer metastasis.[30] Treatment with EGCG (20 μM) was shown to down-regulate MMP-2 expression in breast cancer cells in a dose and time-dependent manner.[31] EGCG was also documented to inhibit cell motility in lung cancer cell lines by reducing membrane fluidity, which resulted in decreased metastatic potential.[32]

The current literature counts up to 42 in vitro studies and 13 studies of mouse xenograft models where the therapeutic supplementation of anticancer drugs with GTP led to a synergistic effect on the inhibition of tumor development.[33] The tumor volume was reduced by 70.3% in the combination of EGCG with anticancer drugs, while EGCG or GTE treatment alone was slightly less effective than in combination with anticancer drugs.[34] 5-Fluorouracil, cisplatin, and docetaxel

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Table 3. Anticardiovascular Activity of Green Tea and Its Polyphenols

in vitro	in vivo	compound	observed effects	reference
	volunteers without history of stroke, coronary heart disease, or cancer	green tea	↓CVD mortality	40
	patients with coronary artery disease	EGCG	↑ endothelial function	41
			↓ endothelial dysfunction	
	patients with or without coronary heart disease (CHD)	green tea	↓ CHD risk	43
			↓ hyperlipidemia and total cholesterol	
	male Sprague–Dawley rats	EGCG	↓ cardiac hypertrophy formation	45
			↑ bcl-2 protein, SOD, and GPx	
			↓ p53 protein, MDA content, and SBP	
	male Sprague–Dawley rats	EGCG	↓ ROS	46
			restored Ca^{2+} homeostasis	
			prevented myocyte apoptosis	
rat heart cardiomyoblast cells		EGCG	↑ telomere repeat-binding factor 2	
			↓ telomere atrrition	48
			↓ p53 expression	
			antiapoptotic effect	
	male Sprague–Dawley rats	EGCG	↑ telomere repeat-binding factor 2	49
			↓ telomere attrition and p53 expression	
human aortic endothelial cells		EGCG	↓ ET-1 synthesis and secretion	51
			↑ NO production	
human umbilical vein endothelial cells		EGCG	↓ membrane translocation of Rac-1 and p47phox	52
			↓ NADPH oxidase	
			↓ ROS generation	
			↑ Akt activation and antioxidant enzymes	
	male and female volunteers	GTE	↓ oxidation of low-density lipoprotein(LDL)	53
human aortic endothelial cells		EGCG	↓ intracellular Ca^{2+}	54
			↑ Nrf-2 expression	
			↑ HO-1 mRNA and protein	
rabbit platelets	male Sprague–Dawley rats	EGCG, EGC	↓ PLCg2 phosphorylation, AA liberation, and serotonin secretion; ↑PGD2	56
	Sprague–Dawley rats	EGCG	↓ NFκB activation	57
			↓ CTGF expression	
	male Sprague–Dawley rats	EGCG	↓ lipid peroxidation	59
			↑ activities of SOD, CAT, and GPx	
			free radical scavenger	
			restored mitochondrial function	
	male albino Wistar rats	EGCG	↓ lysosomal enzymes	60
			↓ lipid peroxidation	
			preserved membrane integrity	
	male Sprague–Dawley rats	EGCG	↓ caspase-3	61
			↓ lipid peroxidation	
			↑ SOD, CAT, and bcl-2 expressions	
			↓ left ventricular end diastolic pressure	
			↑ left ventricular developed pressure and coronary flow	
	male spontaneously hypertensive rats	EGCG	↓ infarct size	62
			improved cardiac hemodynamics	
	heart failure (HF) rats	EGCG	↑ left ventricular end diastolic pressure	63
			↑ mean blood pressure	
			↑ heart weight/body weight	
			↑ posterior wall thickness	
			↓ left ventricular systolic pressure	
			↓ maximum rate of left ventricular pressure rise (+ dP/dtmax)	
			↓ maximum rate of left ventricular pressure	
			↓ G-protein-coupled receptor kinases (GRK2) and β1-adrenoceptors	

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were the most effective drug in the inhibition of cell proliferation and apoptosis. In a study by Wang et al.,[35] tumor cell invasion was significantly reduced when EGCG, quercetin, and docetaxel were used in combination on two prostate cancer stem cell (CSC) lines. The combined use of EGCG and 5-Fluorouracil or cisplatin were shown to reduce the weight of tumors formed by CSC derived from the head, neck, colorectum, and nasopharynx.[36−38] As the agonist of 67 kDa laminin receptor (67LR), EGCG was reported to promote the apoptosis of tumor cells and the polyethylene glycol (PEG) EGCG combined liposome increased the targeted capacity on tumor cell membranes with the effective ability to inhibit the tumor growing.[39] Compared with EGCG modified liposome, the PEG-EGCG modified liposome had a longer circulation time in blood, which also promoted the antitumor activity. The activator protein-1 (AP-1) could regulate the transformation of tumor cells and the EGCG showed inhibitory effect on AP-1 protein.[40] In addition, the EGCG acetylated derivatives have greater affinity with AP-1 protein on the target site of Ser 278, Asp 163, Asp 170, Arg 281, and Arg 288 by hydrogen bonds interactions.[41] The inhibition of AP-1 protein could further up regulate the tumor suppressor gene p53 along with the reducing effect on tumor activity. Due to the crosstalk between GTP-induced cell signaling pathways, GTE or GTP were both reported to effectively prevent the early stages of cancer, while the combined use of EGCG, EGCG derivatives and anticancer drugs exert synergistic inhibition on the proliferation of CSC, which altogether represent promising therapeutic approaches for human cancers.

Anticardiovascular Activity. Cardiovascular diseases (CVD) are responsible for more than 50% of the global mortality.[42] In a cohort study of 40 530 participants from Northeastern Japan, it was shown that regular green tea consumption was inversely associated with mortality due to CVD.[43] Interestingly, this inverse association was more favorable in women, showing that those who consumed five or more cups (≥500 mL) per day had lowered their risk for CVD death by 31% compared to those who consumed less than one cup (100 mL) per day.[44] In a recent survey conducted under the umbrella of the Shanghai Health Study, similar results were concluded in that green tea consumption was inversely associated with risks of all-cause and CVD mortality in middle-aged and elderly adults, especially in nonsmoker individuals.[45] In a study by Pang et al.,[46] the risk of coronary heart disease (CHD) was also decreased by the reduction of hyperlipidemia and total cholesterol in patients reporting regular green tea consumption habits (Table 3).

In reference to the anticardiovascular activity of GTP, it has been well documented that the generation of endothelial cell dysfunction and CVD are closely associated with ROS production in vascular endothelial cells, hence the antioxidant properties of GTP are certainly non-negligible. Elevated concentrations of NADPH oxidase, the major source of intracellular ROS in vascular endothelial cells, promotes the onset and development of hypertension and atherosclerosis.[47] EGCG results showed that the vascular-protective effect were mediated through suppression of NADPH oxidase production by inhibition of angiotensin II (AngII)-induced expression of $p47_{phox}$ (i.e., the regulatory subunit of NADPH oxidase) in a dose-dependent manner.[47] In a study by Sheng et al.,[48] EGCG has shown to exert cardioprotective effects by inhibiting the formation of cardiac hypertrophy through regulation of Bcl-2 and p53 proteins, which results in a decreased systolic blood pressure and increased activity of SOD and GPx.[48] Zheng et al.,[49] demonstrated the ability of EGCG to attenuate doxorubicin-induced myocyte toxicity and prevent myocyte apoptosis through restoration of Ca^{2+} homeostasis and inhibition of ROS production. Telomere dysfunction activates p53- mediated cellular growth arrest and cardiomyocyte apoptosis to drive a functional decline in the heart.[50] The antiapoptotic effect of EGCG are mediated through inhibition of ROS-induced telomere attrition by upregulating the expression of telomere repeat-binding factor 2 while down-regulating p53 in H9c2 cells.[51] In vivo, the same antiapoptotic effects were described in aortic constriction rat models.[52]

In addition, endothelial cell dysfunction can also be induced by lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), that is, the oxidized low-density lipoprotein (oxLDL) receptor of endothelial cells, which promotes the expression of endothelin-1 (ET-1), a vasoconstrictor that lead to endothelial dysfunction and prevents the expression of endothelial NOS.[53] Pretreatment with EGCG, in contrast, was shown to decrease ET-1 synthesis and secretion from endothelial cells via Akt- and AMPK-stimulated forkhead box protein O1 regulation of the ET-1 promoter and stimulated NO production.[54] Ou et al.,[55] also reported that EGCG inhibited the oxLDL-induced LOX-1-mediated signaling pathway, by deactivating the membrane translocation of Rac-1 and $p47_{phox}$, inhibiting NADPH oxidase, inhibiting ROS production, and increasing the phosphorylation of Akt. In a human-based study described by Suzuki-Sugihara et al.,[56] the reduced ox-LDL was also observed by the administration of GTE, which was explained by the direct combination by non-conjugated forms in LDL particle. Moreover, in vascular endothelial cells, EGCG was shown to upregulate the expression of Nrf-2 which in turn drives the expression of heme oxygenase-1 (HO-1) resulting in increased HO-1 mRNA and protein expression and results in the maintenance of vascular homeostasis.[57]

Activated platelet, triggered by the subendothelial matrix such as collagen and thrombin, initiates thrombus formation in response to blood vessel damage, hence promoting the generation of atherothrombotic disease.[58] The antithrombotic and antiplatelet activities of EGCG were demonstrated to be associated with inhibition on arterial thrombus formation along with suppression on serotonin secretion, and collagen- and arachidonic acid-induced platelet aggregation.[59] Excessive collagen and fibronectin production contribute to the development of cardiac fibrosis with elevated connective tissue growth factor (CTGF). EGCG was also documented to attenuate the overexpression of AngII-induced CTGF in fibroblast by blocking the NF-κB pathway.[60]

Myocardial infarction (MI) is the main cause of coronary heart disease mortality in the Western world.[61] According to a study reported by Devika and Prince,[62] the oral administration of EGCG (30 mg/kg BW) significantly prevented the development of MI by regulating the activity of SOD, CAT, and GPx in the cardiac mitochondria of an isoproterenol-induced MI rat model. Additionally, EGCG pretreatment (30 mg/kg BW) could preserve membrane integrity, and significantly reduce the activities of lysosomal enzymes both in the serum and in the myocardium by its ability to prevent lipid peroxidation.[63] Moreover, EGCG was documented for its effect on decreasing the left ventricular end diastolic pressures and its increasing influence on the left ventricular pressure and coronary flow by regulation of SOD, CAT, and Bcl-2

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activities.[64] The acute NO-dependent vasodilator activity of EGCG significantly reduced the size of the infarction and improved cardiac hemodynamics, endothelial and cardiac function in Langendorff-perfused hearts exposed to I/R injury.[65] In a study by Zhang et al.,[66] the administration of EGCG in the heart failure rats showed improved cardiac function resulting from increased left ventricular end diastolic pressure, increased posterior wall thickness and decreased left ventricular systolic pressure. The maximum rate of left ventricular pressure rise and fall (+ dP/dt max), which would be related to the inhibition of the transfer membrane of G-protein-coupled receptor kinases as well as the desensitization of β1-adrenoceptors. In a study by Kim et al.,[67] the stimulation of autophagic flux was investigated in aortic endothelial cells in the presence of EGCG. This promoted the colocalization of lipid droplets and lysosome and a decreased accumulation of lipids. As shown in Figure 2, EGCG gets involved in multiple signaling pathways including PI3K/Akt, Nrf-2/Keap1, AMPK, and Wnt/β-catenin along with regulating the expression of transcription factors in the nucleus. Among them, the EGCG inhibits the phosphorylation of PI3K/Akt pathway and promotes the release of Nrf2 from the complex of Nrf-2/Keap1, which are the key paths to increase the antioxidant capacity of organisms. As the antagonist of Wnt protein, the release of β-catenin could be inhibited by EGCG, which might be another path for decreasing inflammation and apoptosis in cardiovascular dysfunction. For most of the study, EGCG exhibits to block the NF-κB pathway, which is related with the antioxidant, antiapoptotic, and autophagy properties.

Antiobesity and Antidiabetic Effects. Epidemiological studies have observed that the consumption of green tea may lead to decreased body weight, body fat control as well as improved metabolism of glucose and lipid.[68−70] In a previous clinical trial, the consumption of EGCG (800 mg/day, for 8 weeks) was shown to help decrease the body weight of obese men aged between 40 and 65 years of age.[71] In a short-term supplementation study with GTE (2 or 7 days), the authors reported an attenuated glucose and insulin response among obese people with exercise habits. The health benefits of green tea were explained by their effect on promoting insulin sensitivity and altering the expression of glucose transporters.[72] In another double-blind, placebo-controlled clinical trial, the weight loss was found to be significant upon ingestion of a high-dose of EGCG (856.8 mg/d) and was associated with increased adiponectin secretion and reduced levels of cholesterol and plasma LDL.[73] In an animal study, the administration of catechins and EGCG was shown to minimize high fat diet-induced obesity via the promotion of fat oxidation and decreased leptin levels as well as energy absorption.[74] In the senescence-accelerated *mouse* prone 8 (*SAMP8*) mouse model, a 12-week EGCG treatment successfully reduced blood glucose concentrations compared with the normal aging group.[75] In the skeletal muscle of treated mice, PI3K-AKT signaling was detected on the basis of the increased expression glucose transporter 4 (GLU4) and AMPKα activation.[75]Simi-Similar results were confirmed by a study by Wakagi et al.,[76] where the sensitivity of insulin and the activation of AMPK and PI3K-induced pathway were observed in L6 cell cultures and in the muscle of ICR mice. According to a study by Zhang et al.,[77] the intake of GTP led to modulation of the gut microflora in obese mice and metagenomic analysis determined that the ratio *Firmicutes/Bacteroidetes* had decreased. In the treatment group, the gene of ATP-binding cassette transporters in KEGG pathway and amino acid biosynthesis was much more enriched after 8 weeks intervention by GTP.[77] These results indicate that GTP intake may result in more balanced environment to promote the development of gut microbiota, and modulate the metabolic pathway to maintain a healthy status.

In line with their effect on the control of body weight and blood glucose, EGCG and GTP were shown to prevent obesity-induced chronic inflammation or other diseases.[78,79] As an agonist of the 67LR, EGCG can decrease the expression of toll-like receptor 4 by upregulating expression of the E3 ubiquitin protein ring finger receptor in adipose tissue, which prevents the release of pro-inflammatory cytokines.[79] In a study by Coia et al.,[80] GTP-treated mice maintained a healthy body weight, the ratio in liver/body weight and the lower enzymatic levels of aspartate aminotransferase and alanine aminotransferase by the up-regulation on CD^{4+} mediated apoptosis. The decreased expression of Ki67 and increased apoptosis observed in GTP-treated mice liver indicate that a vigorous immune response mediated by GTP may be the underlying resistance mechanism behind DNA damage-induced liver disease.

Antiallergic Activity. An allergic reaction is an overt immune response to antigens, which is generally found in the environment or in food products. In the pathophysiology of allergy, the symptoms may be alleviated by acting upon the proliferation of immune cells or upon desensitization to the allergen.[81] The antiallergic activity of polyphenols may occur at two stages: either during the sensitization phase and/or upon re-exposure to the allergen. First, polyphenols might interact with allergenic proteins to form hypoallergenic insoluble complexes, hence preventing cognate recognition by dendritic cells. The polyphenols might also modulate maturation of dendritic cells, inhibit the proliferation and cytokine production of T cells or promote antibody production by plasma cells.[82] Recent studies have investigated the antiallergic properties of GTP. Maeda-Yamamoto et al.,[83] reported that the consecutive consumption of "*Benifuuki*" green tea for one month could attenuate symptoms in individuals suffering from Japanese cedar pollinosis, without affecting the total serum iron content and IgG antibody titer in seasonal rhinitis.

Recently, a double-blind, randomized, placebo-controlled trial was conducted, involving 51 adults presenting Japanese cedar pollinosis.[84] During the pollen season (December 2007 through March 2008), these subjects were randomly split into two: one group was asked to drink 700 mL of "*Benifuuki*" green tea i.e., containing O-methylated EGCG, while the second group (placebo) was asked to consume the same volume of "*Yabukita*" green tea i.e., not containing O-methylated EGCG. The symptoms of runny nose, itchy eyes, and tearing were significantly reduced in the "*Benifuuki*" green tea group compared to the "*Yabukita*" group. Pollen-exposure-induced peripheral eosinophil recruitment/activation was also suppressed in the presence of "*Benifuuki*" green tea, which suggests that consumption of "*Benifuuki*" green tea has great potential as an alternative strategy for the treatment of seasonal allergic rhinitis.[84]

In animal studies, the antianaphylactic effect of GTE was demonstrated to be associated with inhibition of mast cell activation in a dose-dependent manner.[82] Compound 48/80 triggers the release of histamine through a G-protein-induced signal transduction pathway. In the presence of GTE, the disruption of rat mesenteric mast cells by compound 48/80

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was significantly inhibited. In an allergic rhinitis mouse model, the oral administration of EGCG was shown to decrease the occurrence of nasal rubbing and the number of sneezes.[85] The level of immunoglobulin E (IgE) and histamine were also lower in the EGCG-treated mice, as were the concentrations of proinflammatory cytokines (i.e., interleukin (IL)-1β, IL-4, and IL-6). Using the same mouse model, Yu-Lian et al.,[86] investigated the antiallergic activity of two kinds of GTE. The oral administration of GTE A (containing EGCG) and GTE B (containing both EGCG and EGCG′′Me) both led to remarkable inhibitory effects on allergic symptoms and eosinophil infiltration in nasal tissue. In the GTE A-fed group, the expression of IL-4, -5, and -10 cytokines and the IgG1 level were significantly lower, while the IgG2a levels were significantly higher compared with the positive control allergic rhinitis group. In the GTE B-fed group, antigen-specific IgE production as well as systemic and local inflammation were all inhibited. The suppression of pro-inflammatory cytokines and allergen-specific IgE production may be the main mechanisms underlying the antiallergic properties of GTE.[86]

Neuroprotective effect. A number of clinical and basic research studies support the hypothesis that ROS and an inflammatory process lead to a cascade response resulting in neurodegenerative disorders including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and other neurodegenerative diseases.[87] EGCG was reported to prevent the depletion of striatal dopamine and substantia nigra in mice treated with a parkinsonism-inducing neurotoxin (*N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine).[88] In mice brain mitochondrial membranes tissue and synaptosomes, the iron-ascorbate induced lipid peroxidation was decreased by the addition of GTP in mouse models.[88,89] Wu et al.,[90] investigated the effects of GTE and EGCG in cerebral ischemic rat models to determine whether they were able to prevent ROS production and reduce neuronal damage. Upon 7 day administration, the levels of glutathione and SOD activity measured in the cerebral cortex and the hippocampus regions were increased significantly. In BV-2 microglial cell cultures, the presence of GTE and EGCG led to a reduction in the production of lipopolysaccharide-induced nitric oxide, along with a reduction in nitric oxide synthase and cyclooxygenase-2 expression, suggesting that the neuroprotective effect observed are tightly associated with a reduction of oxidative stress and neuroinflammation.[90] EGCG was also investigated for its binding properties to cell signaling proteins related to neurodegenerative diseases. In a study by Ehrnhoefer et al.,[91] the binding between EGCG and unfolded polypeptides was shown to inhibit the fibrinogenesis of α-synuclein and amyloid β and thus prevent their conversion into toxic aggregation intermediates. Through activation of protein kinase C pathway, EGCG was reported to directly interact with metal-amyloid β and then form a ternary EGCG-A complex in rat cortical neurons, suggesting that the antiamyloidogenic activity of EGCG have a biased effect toward metal-amyloid β species.[92]

Gut Health-Promoting Properties. The gut is often considered as the second most important vital organ after the brain.[93] The gastrointestinal system plays a vital role on the interaction between immune system and diverse external factors including poisonous substances, pollutants, and beneficial as well as pathogenic microorganisms.[94] In a previous study, the intake of GTP was reported to modulate the diversity and composition of gut microbiota by improving the growth of beneficial microorganism, that is, *Bifidobacterium spp.*, *Lactobacillus spp.*, and *Clostridium coccoides*−*Eubacterium rectal*,, while inhibiting the proliferation of pathogenic bacterial species, that is, *Clostridium perfringens*, *Clostridium difficile*, *Bacteroides spp.*, *E.coli O157*, *H7*, and *H. pylor*, which would in turn regulate the health of the host.[95,96] EGCG and ECG were documented for their strong antibacterial activity against pathogenic species, suggesting a linkage between their structure and functional properties.[97] The mechanism underlying the remarkable antibacterial activity of GTP may be explained by their binding on bacterial cell membranes, damage to the lipid bilayer bacterial membrane, and promotion of the production of hydrogen peroxide, which will alter the cell membrane permeability and suppress the growth and proliferation of potentially pathogenic bacterial species.[98,99] GTP is metabolized in the intestinal compartment to generate small metabolites such as phenolic acid, acetic acid, propionic acid, and succinic acid, which may also exert biological effect on the gut microbiota.[100] In the colonic digestive tract, *Bacteroidetes* and *Firmicutes* are the main groups acting on the metabolism of dietary fiber and polyphenols involving a complex metabolic energy-harvesting dynamic where a reduced ratio of *Firmicutes/Bacteroidetes* might contribute to prevention of obesity as shown in both animal models and human clinical trials.[101,102] In the human clinical trial reported by Ley et al.,[103] obese subjects had fewer *Bacteroidetes* but more *Firmicutes* than lean control subjects. Upon weight loss, the *Firmicutes/Bacteroidetes* ratio was shown to decline with an increasing amount of *Bacteroidetes* and a decreasing amount of *Firmicutes*. This ratio was also shown to be reflective of weight loss. In a long-term rat mouse model entailing the consumption of GTP for a period of 6 month, the amount of *Bacteroidetes* was shown to increase, while the growth of *Firmicutes* was hampered. This was found to be positively correlated with a decrease in total cholesterol, bilirubin, and triglycerides concentrations in plasma.[104] In colorectal cancer patients, the proportion of the *Peptostreptococcaceae* family in the *Fimicutes* was shown to be enriched, suggesting that the anticancer effect of GTP may be related to the regulation of specific types of microorganisms in the intestinal tract.[104,105] *Alistipes* and *Rikenella* (*Rikenellaceae* family), are common members found in the human digestive tract, and their relative proportions were shown to be related with the development of obesity. In the obesity mouse model, the genus *Alistipes* and *Rikenella* were all significantly lower in the high-fat diet while green tea intake resulted in an enrichment in these two genera. Major metabolites of *Alistipes* and *Rikenella*, such as short chain carboxylic acids (i.e., succinic acid, alcohols, acetic acid, and propionic acid) exert biological activity such as improving the functions of gut barrier, promoting formation of tight junctions and cell differentiation as well as upregulation of proglucagon gene expression in intestinal L cells, which altogether can contribute to inhibit the onset of inflammatory bowel disease.[94] *Lachnospiraceae*, a well-known gram-negative, anaerobic bacteria, was also investigated for its ability to prevent *Clostridium difficile* infections and was shown to be negatively associated with obesity.[106] In a study by Liu et al.,[94] the intake of green tea was shown to increase the amount of *Lachnospiraceae* and *Verrucomicrobiaceae* present in the digestive tract resulting in decreased weight gain in high-fat diet fed mice. The *Akkermansia* (*Verrucomicrobiaceae* family) genus, a mucin-degrading bacterium, was reported to regulate gut barrier functions as well as lipopolysaccharide binding protein (LBP) secretion in plasma. GTP-induced modification

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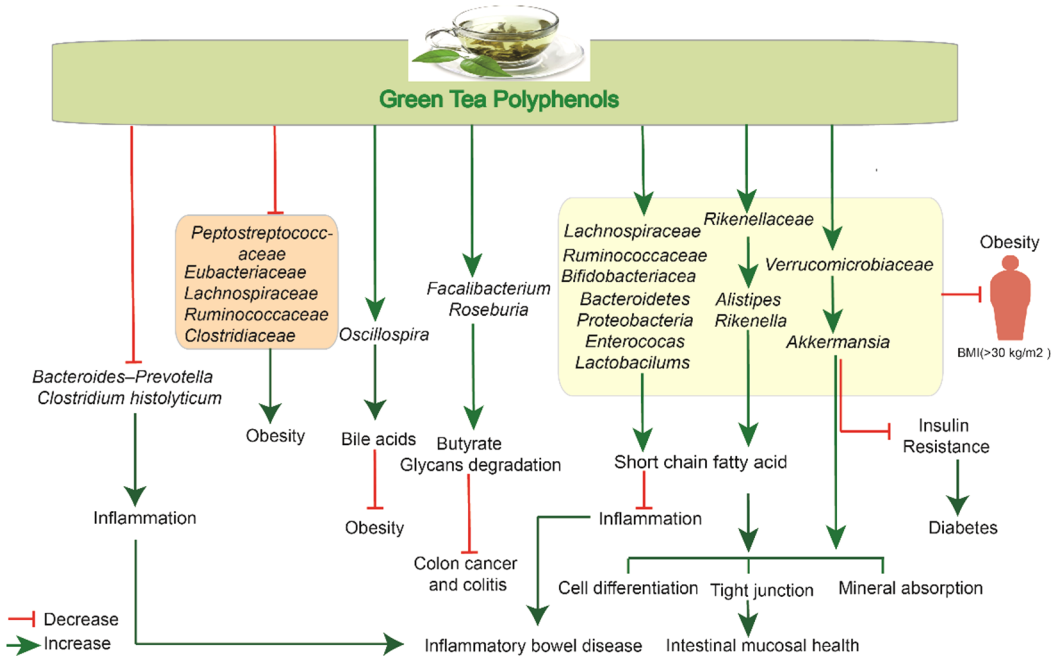

Figure 3. Effect of green tea polyphenols on gut microbiota.

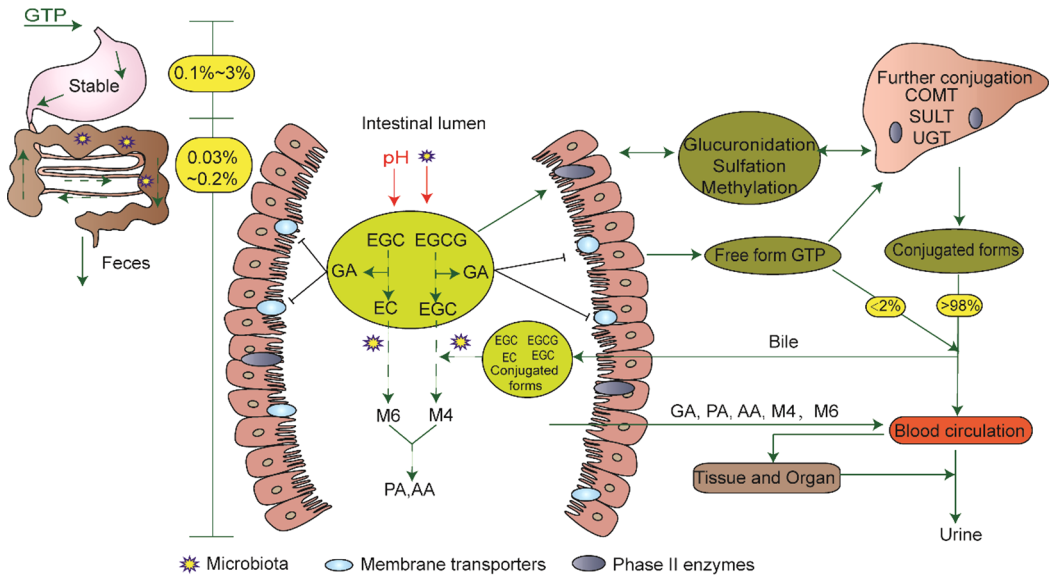

Figure 4. Bioaccessbility, bioavailbility and metablism of green tea polyphenols. GA: gallic acid; PA: phenolic acids; AA: aromatic acids; M6:5-(3′,4′-dihydroxyphenyl)-γ-valerolactone; M4:5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone; membrane transporters (multidrug resistant proteins, ATP-binding cassette transporters, P-glycoprotein); Phase II enzymes (COMT: catechol-O-methyltransferase; SULT: sulfotransferase; UGT: glucuronosyltransferases.

of the gut microbiota and its related health benefits are represented in Figure 3. One study investigating the long-term effect of green tea supplementation in humans failed to show a significant effect on the diversity and composition of the gut microbiota,[107] which is contradictory to previous reports. As such, the mechanisms underlying the effect of GTP on the gut microbiota and its health promoting properties remain to be fully elucidated.

Known from the above studies, most of mechanistic research was carried with the cell model and animal trials, the human intervention trials are still in the initial stage and need further verification. Because of the differences in the condition of health problems, dietary habit, the compliance to test process, and also the genetic background of individual, the unified quantification dose of GTP supplement would be hardly operated, which might be the main reason for mixed results in the recent studies.[93] Thus, depending on the degree of metabolic dysfunction, a long period of large-scale intervention is needed to quantify the optimal doses in supplementation along with the objective to test the beneficial performance on human health.

Bioaccessibility, Bioavailability, and Toxicity. In order to exert a biological effect, polyphenols must first satisfy the criterion of bioavailability, that is, release from the food matrix followed by absorption in the intestinal tract. In this respect, bioaccessibility has been defined as the ratio of substance

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released from the food matrix in the gastrointestinal tract vs the amount available for intestinal absorption whereas bioavailability describes the proportion of ingested substance that enters the systemic circulation.[108] In vitro studies determined that the salivary bioaccessibility of GTP was ranging from 2.83 to 50.39 mg/g in dry weight, while its gastric bioaccessibility ranged from 1.65 to 35.62 mg/g and its intestinal bioaccessibility was distributed like EGCG (2.49 mg/g), ECG (0.35 mg/g), EGC (0.41 mg/g), and EC (0.61 mg/g), which means more than 90% of GTP is lost upon gastric and intestinal digestion.[109] The poor bioavailability of GTP in the intestinal absorption was also widely documented. Upon oral administration, only 13.7% of EGC, 31.2% of EC, and 0.1% of EGCG were reported to be bioavailable directly.[110] In the simulated intestinal absorption system based on a Caco-2 cell model, the bioavailability of polyphenols in green tea was evaluated as EGCG (0.32 mg/g), ECG (0.04 mg/g), EGC (0.05 mg/g), and EC (0.04 mg/g), respectively. The observations suggest that GTP may be able to concentrate in the small intestinal. Moreover, the apical-to-basolateral transportation was shown to be low in Caco-2 cell systems.[109] The limited bioavailability of intact GTP may be related to their polymerization as well as their sensitivity to the digestive enzymatic environment, poor intestinal transportation, rapid metabolism, and plasma clearance in plasma, as shown in Figure 4. The elevated pH in the intestinal tract and the presence of ROS was shown to provide favorable conditions toward the auto-oxidative reactions of catechin and their degradation.[111] In the small intestinal epithelium, transportation of GTP was limited by their affinity to efflux and the basal-to-apical efflux of EC, EGC, ECG, EGCG was all reported to be related with their stimulation on membrane transporters, such as multidrug resistance protein, ATP-binding cassette transporters, P-glycoprotein, and breast cancer resistance proteins.[112,113] Upon absorption, green tea catechins were not only transported in their native structure but also widely metabolized by phase II enzymes—both in the small intestinal and the liver—whereby the catechins are glucuronidated, sulfated, and methylated to form catechins conjugates.[114] Subsequently, catechin conjugates would reach the systemic circulation while most of them would go back to the gastrointestinal tract and eliminated via the bile. Actis-Goretta et al.,[115] found that phase II metabolites of EC were also found in enterocytes, and sulfate conjugates were mainly eliminated by efflux back to the intestinal lumen rather than eliminated via the bile. According to a study by Stalmach et al.,[114] approximately 70% of the ingested GTP was recovered in the colon, of which 37% is found in the form of phase o-linked sulfates and methyl sulfates.

Glucuronidation and sulfation is believed to promote the solubility of catechins and also facilitate their elimination through urine. Thus, the glucuronidated and sulfated conjugates of EGCG, EGC, and EC are commonly detected in human plasma and urine along with their corresponding O-methyl-EGC-O-glucuronides and O-methyl-EC-O-sulfates.[116] In a study by Clarke et al.,[117] the free form of EGCG was found in relatively higher concentrations than those of EGC and ECG in the plasma upon green tea supplementation for a period of 3 h. Upon a long-term treatment of 3 months, a total of 20 green tea catechin metabolites were detected in blister fluid of human skin and the most prominent conjugated forms of EC and EGC were identified as EC-O-sulfate, O-methyl-EC-Osulfate, and O-methyl-EGC-O-sulfate.[117] In the colon, the most abundant catechins may be further catabolized by the microflora into smaller molecular metabolites. EGCG was reported to be widely hydrolyzed leading to the production of EGC and gallic acid by the intestinal microbiota. The EGC may be further degraded into 5-(3′,4′,5′-trihydroxyphenyl)-γ-valerolactone (M4) in the large intestinal compartment.[118] EC are further metabolized into 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone (M6) and are subject to the same metabolic process as EGC. Classically, M4 and M6 are the major catechins catabolites resulting from the ring-fission activity of the intestinal microbiota. They may then be absorbed directly or be further shortened to C6−C1 phenolic and aromatic acids, and eventually enter the blood circulation and be excreted into the urine. Interestingly, gallic acid was shown to be further hydrolyzed to dyrogallol and finally be absorbed in the large intestine.[119] In human urine, a number of phenolic acids identified as 4-hydroxybenzoic acid, hippuric acid, 3-(3-hydroxyphenyl)-3-hydroxypropionic acid, 3-methoxy-4-hydroxyphenylacetic acid, and 4-hydroxyphenylacetic acid, were found which are believed to exert significant biological effects beyond those of their parent compounds.[120]

In order to improve the bioavailability of GTP, nanoparticles were exploited as carrier systems to promote the stability and absorption of catechins. Siddiqui et al.,[121] used polylactic acid (PLA) and polyethylene glycol (PEG) nanoparticles to produce encapsulated EGCG, which were shown to be transported at a 10-fold higher yield than nonencapsulated EGCG. Most importantly, PLA−PEG nanoparticles are biodegradable, and are cleared rapidly by endocytosis, thereby minimizing undesirable cytotoxicity. In a study by Hu et al.,[122] casein phosphopeptides nanoparticles were shown to enhance intestinal permeability and absorption of EGCG. Puligundla et al.[113] proposed that nanoparticle-based delivery systems decrease the exposure of GTP to the gastrointestinal tract, thereby reducing their apparent clearance in the plasma, thus enhancing their biological activity and half-life in the body.

Although the bioavailability of GTP is low, fasting and repeated administration are able to sustain but also elevate the concentrations of polyphenols in the plasma to reach toxic levels.[123] EGCG pretreatment (300 mM) resulted in elevated ROS production and enhanced cell damage and apoptosis.[9] A single dose of EGCG (1500 mg/kg) led to increased levels of plasma alanine aminotransferase, an indicator of liver damage, by 138-fold and reduced the survival of mice by 85%.[123] Hepatic necrosis was also observed after high oral doses of EGCG which was associated with its pro-oxidant effects, inducing H_2O_2 generation and oxidative stress in the liver and the plasma.[124] The hepatotoxicity of EGCG is believed to be related to the activity of its metabolites, which induce oxidative stress in the liver. In the cohort study in Japan, 80% of the population drinks green tea, and more than half of them consume 3 or more cups/day (100 mL/cup), which showed inverse association between green tea consumption and CVD mortality.[125] In a double-blind, placebo-controlled study, a one-year treatment with GTP (600 mg/day) was conducted on 60 male volunteers with high-grade prostate intraepithelial neoplasia and led to a 90% chemoprevention efficacy without any adverse effects.[126] In another double-blind, placebo-controlled clinical trial, the weight loss was found to be significant upon ingestion of a high-dose of EGCG (856.8 mg/day) and was associated with increased adiponectin secretion and reduced levels of cholesterol and plasma LDL.[127] With the differences in experimental design, the formulation of tea used

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or the dosing scheduling was difficult to quantify. However, the 10−29 mg/kg/day supplement of green tea extracts was found to cause liver toxicity in human.[128] Recently, James et al.,[129] reported that pretreatment with dietary EGCG (3.2 mg/g diet, 2 weeks) in mice could reduce the high dose (750 mg/kg, body weight, 3 days) induced hepatotoxicity, and increase the glutathione peroxidase expression. Thus, dietary treatment with EGCG might be regarded as a strategy to mitigate the toxic potential of high dose oral intake of EGCG.

In conclusion, the anticardiovascular disease, anticancer, and antiobesity properties of GTP have been largely supported by a myriad of investigations. Their beneficial effects on a diverse panel of health disorders as well as the mechanisms associated with GTP encompass stimulation of Nrf2, Akt, and NF-κB signaling pathways. As a natural product, GTP was also documented for its ability to regulate the diversity of the gut microbiota, promoting gut health and preventing chronic metabolic diseases. Upon daily administration, the adverse effects of GTP were found to be limited; however, a better knowledge of their biotoxicity at higher dosage remains to be determined. The effect of the food matrix on the health-promoting effect of green tea remains to be ascertained through larger sample size human trials. Further investigations are needed to determine the safe range and appropriate amounts of GTP consumed in humans and to develop innovative and safe strategies to enhance the absorption of GTP, particularly EGCG. Overall, green tea and their polyphenols are beneficial to human health; however, their mechanisms of action remain to be fully elucidated.

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ABBREVIATIONS USED

ACF, aberrant crypt foci; AMPK, AMP-activated protein kinase; AngII, angiotensin II; AOM, azoxymethane; AP-1, activator protein-1; BLM, Bleomycin; CAT, catalase; COX-2, cyclooxygenase-2; CSC, cancer stem cells; CTGF, connective tissue growth factor; CVD, cardiovascular disease; DPPH, 2,2-diphenyl-1-picrylhydrazyl; EC, (−)-epicatechin; ECG, (−)-epicatechin-3- gallate; EGC, (−)-epigallocatechin; EGCG, (−)-epigallocatechin-3-gallate; ET-1, endothelin-1; GLU4, glucose transporter 4; GPx, glutathione peroxidase; GTE, green tea extracts; GTP, green tea polyphenols; HO-1, Hemeoxygenase-1; IgE, immunoglobulin E; iNOS, nitric oxide synthase; Keap1, kelch- like ECH-associated protein 1; LOX-1, lectin-like oxidized low-density lipoprotein receptor-1; LR, laminin receptor; M_1dG, 3-(2-deoxy-β-D- erythro-pentofuranosyl)pyrimido[1,2-α]purin-10(3*H*)-one; MDA, malondialdehyde; MMP-2, Matrix metalloproteinase-2; NADPH, Nicotinamide adenine dinucleotide phosphate; NF-κB, transcription factor nuclear factor kappa B; NOS, nitric oxide synthase; Nrf2, NF-E2-related factor 2; OxLDL, oxidized low-density lipoprotein; PEG, polyethylene glycol; PPE, polyphenon E; ROS, reactive oxygen species; RXR, retinoid X receptor; SOD, Superoxide dismutase

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