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A Review of the Health Effects of Green Tea Catechins in In Vivo Animal Models[1]

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ABSTRACT There is good evidence from in vitro studies that green tea catechins have a role in protection against degenerative diseases. However, the concentrations used in vitro are often higher than those found in animal or human plasma, and so in vivo evidence is required to demonstrate any protective effect of catechins. This article summarizes the most interesting in vivo animal studies on the protective effects of green tea catechins against biomarkers for cancer, cardiovascular disease, and other degenerative diseases. Generally, most studies using animal models show that consumption of green tea (catechins) provides some protection, although most studies have not examined dose response. Tea catechins could act as antitumorigenic agents and as immune modulators in immunodysfunction caused by transplanted tumors or by carcinogen treatment. Green tea has antiproliferative activity in hepatoma cells and hypolipidemic activity in hepatoma-treated rats, and some studies report that it prevents hepatoxicity. It could act as a preventive agent against mammary cancer postinitiation. Nevertheless, the implications of green tea catechins in preventing metastasis have not been clearly established. Long-term feeding of tea catechins could be beneficial for the suppression of high-fat diet–induced obesity by modulating lipid metabolism, could have a beneficial effect against lipid and glucose metabolism disorders implicated in type 2 diabetes, and could also reduce the risk of coronary disease. Further investigations on mechanisms, the nature of the active compounds, and appropriate dose levels are needed. J. Nutr. 134: 3431S–3440S, 2004.

KEY WORDS: • *green tea* • *catechin* • *epigallocatechin gallate* • *in vivo animal studies* • *cancer* • *cardiovascular disease*

Tea is one of the most popular beverages consumed worldwide. Tea, from the plant *Camellia sinensis*, is consumed in different parts of the world as green, black, or oolong tea. Green tea is favored in Japan and China, and initial research on the benefits of green tea was carried out in these countries because of local customs. Tea contains many compounds, especially polyphenols, and epidemiological studies show that polyphenolic compounds present in tea reduce the risk of a variety of diseases (1–4).

Green and black tea are processed differently during manufacturing. To produce green tea, freshly harvested leaves are steamed to prevent fermentation, yielding a dry, stable product. Catechins are the main compounds in green tea; they consist of (−)-epicatechin, (−)-epicatechin-3-gallate (ECg),[3] (−)-epigallocatechin, and (−)-epigallocatechin-3-gallate (EGCg) (5). To produce black tea, the fresh leaves are allowed to wither, decreasing their moisture content, until their weight is ~55% of the original leaf weight. The withered leaves are then rolled and crushed, initiating fermentation of polyphenols. This fermentation converts catechin to theaflavins and thearubigins, consequently decreasing the catechin content.

Many in vitro studies on catechins report mechanisms consistent with protection against degenerative diseases (6–9). Nevertheless, many of these studies used high concentrations of catechin and thus do not reflect typical catechin concentrations found in animal or human plasma. It is difficult to extrapolate these results to in vivo situations. Moreover, nongalloylated catechins are present in plasma as conjugated forms (10–12), except for EGCg and ECg, which are significantly unconjugated (13). However, because of the lack of conjugated forms as standards or test compounds, it is not possible to test the in vitro biological effects of the conjugates.

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[3] Abbreviations used: AOM, azoxymethane; CYP, cytochrome P450; DENA, diethylnitrosamine; DMBA, 7,12-dimethylbenz[a]anthracene; DMH, dimethylhydrazine; ECg, (−)-epicatechin-3-gallate; EGCg, epigallocatechin gallate; ENNG, *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine; GTE, green tea extract; IQ, 2-amino-3-methylimidazol(4,5-*f*)quinoline; MNNG, methyl-*N*′-nitro-*N*-nitrosoguanidine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PGI_2, prostacyclin I_2; SOD, superoxide dismutase; TRAMP, transgenic adenocarcinoma of the mouse prostate; TXA_2, thromboxane A_2; UDP-GT, UDP-glucuronosyltransferase.

TABLE 1

Summary of studies on effects of green tea catechins on cancer in animal models

Ingested dose/d	EGCg equivalent	Species	Stress	Duration *d*	Subjects/ group	Biomarkers affected	Biomarkers not affected	Reference
GTE (1.5%, wt:v)		Hamster	DMBA (0.5%)	105	16	↓ Oral tumor burden ↓ Dysplasia and oral carcinoma ↓ Micronuclei formation ↓ Proliferating cell nuclear antigen		14
GTE (6 g/L)		Hamster	DMBA (0.5%)	126	28	↓ Number of oral tumors ↓ Volume of oral tumors ↓ Squamous cell carcinoma	Microvessel density	15
GTE (0.1%)	15 mg/kg	Mouse	ENNG (100 mg/L)	84	Not given	↓ Duodenal tumors		16
GTE (0.025%)	3.7 mg/kg	Mouse	ENNG (100 mg/L)	84	Not given	↓ Duodenal tumors		16
EGCg	5 mg/kg	Mouse	ENNG (100 mg/L)	84	Not given	↓ Duodenal tumors		16
EGCg	50 mg/kg	Rat	MNNG (80 mg/L)	112	Not given	↓ Incidence of gastric carcinogenesis; number of adenocarcinomas, adenomas, adenomatous hyperplasias		16
GTE (0.01%)	1.8 mg/kg	Rat	AOM (7.4 mg/kg)	112	Not given	↓ Colon tumors		16
GTE (0.1%)	18 mg/kg	Rat	AOM (7.4 mg/kg)	112	Not given	↓ Colon tumors		16
Green tea (2%, wt:v)		Rat	DMH (20 mg/kg)	224	42	↓ Aberrant crypt foci ↓ Number of tumors ↓ Tumor volume ↓ Proliferating cell nuclear antigen ↓ Ras-p21 and Bcl-2 expression ↑ Bax expression		17
GTE (0.05%, wt:v)		Rat	DMH (100 mg/kg)	10	20	↓ Colonic mucosal lipid hyperoxidation		18
GTE (0.1%)		Rat	DMH (40 mg/kg)	231	21	↑ Volume of intestinal tumors	Multiplicity and/or incidences of intestinal adenomas Multiplicity and incidences of intestinal carcinomas	19
GTE (0.05%, wt:v)		Rat	DMH (25 mg/kg)	10	8	↓ DNA damage		20
GTE (2%, wt:v)		Rat	DMH (20 mg/kg)	112	15	↓ Aberrant crypt foci in intestine ↓ Proliferating cell nuclear antigen ↓ Ras-p21 expression		21
GTE (50 mg/kg)		Rat	Azoxymethane (74 mg/kg)	112	20		Colorectal tumors Incidence of tumors Level of dysplasia Cancer invasiveness	22
GTE (2%, wt:v)	56 mg/kg	Mouse	NNK (56 μmol/kg)	91	25	↓ Number of lung tumors		23
GTE (1%, wt:v)		Mouse	NNK (100 mg/kg)	28		Immune parameters normalized		24
EGCg (wt:v)	56 mg/kg	Mouse	NNK (56 μmol/kg)	91	25	↓ Number of lung tumors		23
Green tea	0.56 mg/mL	Mouse	Subcutaneous injection LL2-Lu3 cells (10^6)	252	5	↓ Reduction of lung tumors	Lung tumor weight	25
GTE (1%, wt:v)		Mouse	Lewis lung carcinoma transplantation	21		↓ Lung tumor weight ↓ Thymus weight ↑ CD4	CD8	24
Green tea (0.63%, wt:v)	122 g/L	Mouse	DENA (50 μg/kg)	280	15	↓ Number of liver tumors ↓ Hepatic adenomas ↓ Number of diameter for tumors ↓ Number and volume of liver foci ↓ Lung adenoma multiplicity ↓ Number of lung adenomas		26
Green tea (1.25%, wt:v)	245 g/L	Mouse	DENA (50 μg/kg)	280	15	↓ Number of liver tumors ↓ Hepatic adenomas ↓ Number of diameter for tumors ↓ Number and volume of liver foci ↓ Lung adenoma multiplicity ↓ Number of lung adenomas		26

Ingested dose/d	EGCg equivalent	Species	Stress	Duration *d*	Subjects/ group	Biomarkers affected	Biomarkers not affected	Reference
GTE (0.1%, wt:v)	0.085%	Rat	DENA (200 mg/kg)	70	10	↓ Liver DNA damage during carcinogenesis		27
GTE (1%)		Rat	DENA (200 mg/kg)	42	13	↑ Liver weight ↓ Glutathione S-transferase		28 29
GTE (2%, wt:v)		Rat	2-NP[1] (120 mg/kg)	14	5	↓ Cell proliferation in the liver		29
Green tea (2%, wt:v)	410 g/L	Rat	2-NP (100 mg/kg)	14	5	↓ Lipid peroxide levels ↓ Lactate dehydrogenase ↓ Alanine amino transferase		30
Green tea (0.5%, wt:v)	12.4%	Rat	Aflatoxin (25 mg/kg) + CCl_4 (0.8 mL/kg)	24	12	↓ Glutathione S-transferase (liver) ↓ Lipid peroxide level (liver) ↓ Fibrosis		31
GTE (2%, wt:wt)		Rat	Subcutaneous injection of AH109A cells (10^5)	14	10	↓ Weight of liver primary tumor ↓ Total plasma cholesterol ↑ HDL cholesterol ↓ VLDL + LDL cholesterol ↓ Atherogenic index ↓ Serum triglycerides ↑ Excreted fecal biliary feces ↑ Weight of dried feces	Serum lipid peroxide	32
GTE (0.1%, wt:v)	0.085%	Rat	Choline-deficient diet	70	10	↓ Liver DNA damage during carcinogenesis	Liver tissue damage Plasma alanine aminotransferase	27
GTE (0.5% of diet)	0.29%	Rat (female)	DMBA (50 mg/kg)	161	14		Multiplicity of mammary tumors	33
EGCG (0.5%)	0.4%	Rat (female)	DMBA (50 mg/kg)	161	14		Multiplicity of mammary tumors	33
GTE (1%)		Rat (female)	DMBA (25 mg/kg)	252	20	↓ Total mammary tumors	Size mammary tumors Induction of histopathological mammary tumors	34
EGCg (1%)		Nude mouse	Transplantation RIII/MG cells (10^5)	140	3	↓ Growth of precancerous RIII/MG cells No tumor formation	Body weight	35
GTE (0.3%, wt:v)		Rat (female)		119	15	↑ Latency of first mammary tumors ↓ Mammary tumor weight ↓ Number of invasive mammary malignant tumors	Number of noninvasive mammary malignant tumors	36
GTE (0.1%, wt:v)	.62 mg/kg	TRAMP mouse		168	10	↓ Prevention or delay of prostate cancer development ↓ Growth of prostate tumor ↓ Prostate weight ↓ Genitourinary organ weight ↓ Number of apoptotic cells in prostate ↓ Life expectancy		37

[1] Abbreviation: 2-NP, 2-nitropropane.

Thus, animal studies are more relevant for investigating the physiological effects of catechins, but in vitro studies often provide more mechanistic information. This article summarizes the most interesting in vivo animal studies of the biological effects of green tea on biomarkers of chronic disease risk.

In vivo studies of green tea and cancer

Many experimental animal studies using biomarkers of cancer risk or cancer development have tested green tea extract (GTE) or EGCg. Many of these studies report that GTE or EGCg protects against chemical carcinogens in various organs such as intestine, lung, liver, prostate, and breast (see **Table 1** for a summary).

Effects on oral and gastrointestinal cancer. Hamsters were treated with topical 7,12-dimethylbenz[a]anthracene (DMBA) to induce oral tumors in the buccal pouch (14,15). Oral administration of green tea before and until the end of the experiment reduced the mean tumor burden, including the incidence of dysplasia and oral carcinoma (Table 1).

N-ethyl-*N*′-nitro-*N*-nitrosoguanidine (ENNG) and azoxymethane (AOM) cause intestinal or colorectal tumors after chronic administration. Green tea (0.1–2.0% of diet) decreased the number of duodenal or colon tumors induced by the various promoters (16). Dietary ingestion of EGCg, the main compound present in green tea, also decreased the incidence of duodenal tumors (Table 1). In parallel, ingestion of EGCg by rats decreased the incidence of gastric carcinogenesis induced by methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) (Table 1). These findings suggest that green tea catechins and EGCg are useful in preventing gastrointestinal carcinogenesis. Nevertheless, a study performed under similar conditions (with AOM pretreatment and then green tea administration) found that green tea had no effect on colorectal carcinogenesis, but this could be due to differences in ingestion during the studies (22) (Table 1).

Other parameters, such as histological assessment or expression of specific genes, can be measured in animal models of colorectal cancer. Aberrant crypt foci appear in the colonic mucosa of carcinogen-treated animals and represent precursor lesions of chemically induced colon cancer. This assessment permits evaluation of the role of nutritional components and screening of potential new chemopreventive agents. Green tea inhibits aberrant crypt foci and colorectal cancer induced by dimethylhydrazine (DMH) in rats (17,21). 8-Hydroxydeoxyguanidine is a product of DNA damage by oxygen radicals. DNA damage causes misreading of DNA bases, leading to mutagenesis and carcinogenesis; therefore, 8-hydroxydeoxyguanidine is speculated to be a biomarker of oxidative stress–related carcinogenesis. The administration of green tea inhibits DNA damage, as shown by a decrease in 8-hydroxydeoxyguanidine production, suggesting that green tea reduces mutagenesis and carcinogenesis (Table 1) (18,20). Moreover, the activation of ras p-21 represents one of the earliest and most frequently occurring genetic alterations associated with human cancer. Oral feeding with a diet containing 2% green tea suppresses the DMH-induced expression of ras p-21.

Two important mechanisms of action of green tea may be inhibition of cancer cell proliferation and induction of apoptosis. After ingestion, green tea catechins are present as native forms in the digestive tract. Because they are not completely absorbed by the gut (38), catechins can be present at high concentrations in the intestinal lumen and in this way can interact directly with duodenal or colon tumors by influencing apoptosis and proliferation.

Effects on lung cancer. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is generally used to induce lung tumorigenesis. Ingestion of green tea (2% of diet) decreased the number of lung tumors induced by NNK in mice, compared with a control group that was not treated with tea (23) (Table 1). This result was confirmed by another experiment in which mice were subcutaneously injected with Lewis lung carcinoma cells (25). Peroral administration of a green tea infusion markedly reduced the number of lung tumors.

An equivalent experiment was conducted with EGCg at the concentration found in green tea (Table 1). The number of tumors decreased, but the decrease was less than with green tea. These observations suggest that EGCg, the major compound of tea, could be the principal but not the only compound responsible for the decrease in tumorigenesis. EGCg might interact synergistically or additively with the other catechins present in green tea, but this has not been demonstrated.

Diethylnitrosamine (DENA) induces lung tumors when injected. Ingestion of green tea during DENA treatment decreased the number of lung tumors in mice at all dosages (Table 1) (26). This suggests a possible association between the chemopreventive activity of tea on lung tumors and the concentration of EGCg in tea.

Treatment with DENA altered immune functions in mice: suppressive modulation, such as humoral immunity and cell immunity, and enhanced modulation, such as nonspecific phagocytosis. Ingestion of green tea returned these immune functions to basal levels (24). Moreover, the transplantation of Lewis lung carcinoma cells into mice decreased the CD_4^+-positive T lymphocytes and CD_4^+:CD_8^+ ratio. Ingestion of green tea improved immune functions and inhibited tumor growth (24).

These results show that tea catechins could act as antitumorigenic agents and as immune modulators in immunodysfunction caused by transplanted tumors or by carcinogen treatment.

Effects on liver cancer. DENA also induces tumors in the liver. Animals treated with DENA and green tea at different concentrations showed a marked decrease in liver tumors (diameter, number, number, and volume of liver foci) (Table 1) (26,28,32). As discussed above, this suggests a possible association between the chemopreventive activity of tea on lung tumors and the concentration of EGCg in tea, but there was no apparent relation between EGCg and liver tumor response.

In the same model, green tea reduced oxidative DNA damage in mice (27) and rats (29,30). The authors suggest that green tea may be a chemopreventive agent for hepatocarcinogenesis in the absence of chronic hepatocyte damage. Similar results were reported in animals treated with aflatoxin; green tea inhibited initiation and promotion steps (Table 1) (31). Moreover, daily ingestion of green tea prevented hepatotoxicity (increase in serum glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase; decrease in hepatic glycogen, serum triglyceride, and lactate dehydrogenase) (Table 1) and cell proliferation in the liver in rats after administration of 2-nitropropane (29,30).

Choline deficiency causes chronic hepatocyte damage in mice, which mimics tumor development in cirrhotic liver tissue. In this model, green tea did not protect against liver tissue damage as assessed by either histology or plasma marker enzyme levels (Table 1). This suggests that green tea might have limited potential to inhibit tumor development in cirrhotic liver tissue. Biological variables were measured after implantation of hepatoma cells in rats with and without ingestion of green tea (32). Green tea markedly suppressed hepatoma-induced hyperlipidemia (hypercholesterolemia and hypertriglyceridemia) (Table 1). Moreover, green tea increased biliary secretion into feces.

These results suggest that green tea has an antiproliferative activity on hepatoma cells, has hypolipidemic activity in hepatoma-treated rats, and also prevents hepatoxicity.

Effects on mammary cancer. The effects of green-tea catechins on mammary cancer were tested in DMBA-treated female rats (33,34) (Table 1). Green tea or EGCg exhibited chemopreventive action on DMBA-induced mammary carcinogenesis only when given in the postinitiation stage, and the effect was not dose dependent. Indeed, green tea ingestion markedly increased the mean latency of tumors and reduced the tumor burden and the number of invasive tumors in rats with DMBA-induced mammary carcinogenesis (36). Green tea administered at the time of transplantation had a similar effect on transplanted mammary cells in mice (Table 1) (36). These results suggest that green tea could act as a preventive agent against mammary cancer postinitiation. Further investigations are required to establish the mechanisms of action, the nature of the active compounds, and the appropriate dose levels.

Effects on prostate cancer. Transgenic adenocarcinoma of the mouse prostate (TRAMP) is one model for prostate cancer that closely mimics progressive forms of the disease in humans. Green tea inhibits the growth and the progression of prostate cancer in such mice (Table 1), and furthermore inhibits metastasis of this cancer to distant organ sites (lymph, lungs, liver, and bone) (37).

Regarding the biological effects of green tea against various cancers, catechin may be a chemopreventive agent at the early stages. Nevertheless, the implications of green tea catechins in preventing metastasis have not been clearly established.

Cardiovascular diseases and green tea

Cardiovascular diseases, principally heart disease and stroke, are the leading cause of mortality in Western countries among both men and women in all racial and ethnic groups. The risk of atherosclerosis is increased by high blood pressure (hypertension), kidney disorders, obesity, diabetes, smoking, excessive alcohol consumption, stress, thyroid and adrenal gland problems, and lipid disorders.

Effects on antioxidant markers and oxidative stress. Antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species, such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals, and peroxynitrite. An imbalance between antioxidants and reactive oxygen species results in oxidative stress, leading to cellular damage. Catechins are hypothesized to help protect against these diseases by contributing, along with antioxidant vitamins (i.e., vitamins C and E) and enzymes [i.e., superoxide dismutase (SOD) and catalase], to the total antioxidant defense system.

In vivo studies show that green tea catechins increase total plasma antioxidant activity (39,40) (**Table 2**). Intake of GTE also increases the activity of SOD in serum and the expression of catalase in the aorta, enzymes implicated in cellular protection against reactive oxygen species (40,41). This action is combined with direct action on oxygen species by a decrease in the nitric oxide plasma concentration (41). Malondialdehyde, a marker of oxidative stress, also decreases after green tea intake (39,50). These results suggest that catechins could have a direct (antioxidant) or indirect (increase of activity or expression) effect.

Because catechins can act as antioxidants in vitro, they might prevent the oxidation of other antioxidants, such as vitamin E. However, ingestion of green tea catechins does not modify the plasma status of vitamins E and C in vivo (40,46,55) (Table 2). Nevertheless, 1 study reports that catechens increase vitamin E concentration in LDL (46) and in this way could protect LDL against peroxidation (39).

Effects on lipid metabolism. Green tea catechins affect lipid metabolism by different pathways and prevent the appearance of atherosclerotic plaque (Table 2). GTE intake decreases the absorption of triglycerides and cholesterol (42,45), and these findings are in accordance with the fact that fat excretion increases (42). Nevertheless, the mechanism remains to be determined. Some studies report that green tea catechins decrease plasma total cholesterol and blood triglyceride levels, but the effects differ among studies (43,44,46) (Table 2). This difference could be due to the different animal models used (i.e., rats, mice, and rabbits) (Table 2). Moreover, regarding the green tea catechin intake levels in these studies, plasma cholesterol apparently decreases only when green tea intake is >0.5% of the diet (Table 2). This suggests that the effect on plasma cholesterol occurs only at high doses. Nevertheless, green tea ingestion decreases LDL cholesterol (39). Concurrently, HDL cholesterol increases, showing that green tea polyphenols exert an antiatherosclerotic effect. This effect is also reported in apolipoprotein E–deficient mice (43).

These results demonstrate that long-term feeding of tea catechins can be beneficial in the suppression of high-fat diet–induced obesity by modulating lipid metabolism. By this mechanism, green tea could possibly reduce the risk of associated diseases, including diabetes and coronary disease.

Effects on carbohydrate metabolism. Type 2 diabetes is a heterogeneous disorder that involves resistance of glucose and lipid metabolism in peripheral tissues to the biological activity of insulin and inadequate insulin secretion by pancreatic β cells. Various animal models and treatments mimic diabetes: Zucker rats (which are genetically obese), injection of streptozotocin or alloxan (which destroys pancreatic β cells), and treatment with sucrose-rich diets (which induces obesity and insulin resistance).

In a study in rats treated with alloxan, green tea decreased serum glucose levels (51), suggesting that catechins interact with glucose metabolism. Moreover, in an oral glucose tolerance test in normal rats, green tea catechins decreased plasma insulin levels but did not affect plasma glucose levels (54). Nevertheless, adipocytes increased glucose uptake, but the interaction between catechins and glucose metabolism is unclear and should be investigated.

In type 2 diabetes, lipid metabolism is modified: plasma and liver triglyceride levels and plasma cholesterol levels are elevated. GTE intake reduced these values in both Zucker rats and rats fed a sucrose-rich diet (52,53). Catechins also reduced plasma triglyceride levels in an oral glucose tolerance test in normal rats (54).

These results suggest that green tea catechins could act as preventive agents and could have a beneficial effect against lipid and glucose metabolism disorders implicated in type 2 diabetes.

Effects on nephropathy. Diabetes is generally accompanied by nephropathy due to microvascular dysfunction or impairment. In normal kidney tissue the production of thromboxane A_2 (TXA_2) and prostacyclin I_2 (PGI_2) is controlled, and the balance between them is important to maintain homeostasis in vivo. A modification of the PGI_2:TXA_2 ratio accelerates thrombogenesis in the renal tubules, increasing the risk of impaired function and atherosclerosis. The production of these compounds depends on the activity of phospholipase A_2 (which is higher in the case of kidney disorders) and the fatty acid composition. Streptozotocin increases the synthesis of TXA_2 and decreases that of PGI_2. Administration of green tea catechins in rats pretreated with streptozotocin decreases the synthesis of TXA_2 and increases that of PGI_2 (47,48) and so returns the ratio to that of untreated rats (Table 2). Kidney function is improved by green tea catechin supplementation as a result of its antithrombogenic action, which in turns controls the arachidonic acid cascade system. This also demonstrates that the glomerular filtration rate is increased (Table 2). One study examined blood variables of glomerular filtration (protein excretion, glucose excretion, and blood nitrogen) in rats treated with cisplatin, a nephropathy inducer (50). Because green tea did not affect the excretion of protein and glucose in urine, the blood nitrogen level was markedly decreased (Table 2). Moreover, in the kidney, SOD and catalase activities were decreased and increased, respectively. Thus, green tea catechins appear to reduce oxidative stress in the kidney.

Effects on vascular disease. Pathogenesis of vascular diseases such as atherosclerosis is 2 to 6 times higher in diabetic subjects than in normal subjects. Green tea catechins normalized the PGI_2:TXA_2 ratio in rats treated with streptozotocin and also suppressed phospholipase A_2 and cyclooxygenase activities (49). These results show that green tea catechins have antithrombotic effects in these models.

Other effects of green tea catechins

Effects on absorption of ions. Tea catechins can affect iron absorption, particularly in groups at risk of iron deficiency (56,57), but their effects on other ions are poorly defined. Green tea ingestion over a long period does not affect the apparent absorption of copper, in contrast to that of zinc, which decreases, and that of manganese, which increases (61) (**Table 3**). However, catechin intake does not affect the plasma concentration of

TABLE 2

Effects of green tea catechins on cardiovascular diseases in animal models

Ingested dose/d	EGCg eq	Species	Stress	Duration *d*	Subjects/ group	Biomarkers affected	Biomarkers not affected	Reference
Green tea (3.5 g/L)		SHRSP[1] rat		20	5	↓ Systolic and diastolic blood pressure ↑ Catalase expression (aorta) ↓ Nitric oxide plasma concentration	Urinary nitric oxide excretion	41
EGCG (1%)		Rat	Dietary cholesterol (5 g/kg diet)	24	8	↓ Total cholesterol in plasma ↓ Hepatic total cholesterol ↑ Increase the fat excretion ↓ Triglyceride and cholesterol absorption	Liver lipid concentration	42
GTE (0.8 g/L; 4 mL/d)	584 g/kg	Mouse Apo (E) deficiency		98	17	↑ Body weight ↓ Atherosclerotic area	Plasma cholesterol Plasma triglycerides	43
GTE (0.5%, wt:wt)	74% of catechin	Mouse C57BL/6 J	High-fat diet (300 g/kg diet)	308	5	↓ Energy intake ↓ Fecal lipids ↓ Liver triglycerides ↓ Plasma total cholesterol ↓ Plasma glucose ↓ Insulin ↓ Leptin ↑ mRNA expression of acyl-CoA oxidase ↑ mRNA expression of medium-chain acyl-CoA dehydrogenase	Liver cholesterol Plasma triglycerides	44
GTE (2.5%)	11.6% of GTE	Rat	Dietary cholesterol (10 g/kg diet)	35	?	↓ LDL peroxidation ↑ Serum antioxidant capacity ↓ Total plasma cholesterol ↓ Plasma free cholesterol ↓ LDL cholesterol ↑ HDL cholesterol		39
GTE (120 mg)	23.8 mg/L	Rat (ovariectomized)		1	5	↓ Cholesterol absorption ↓ α-Tocopherol absorption		45
GTE (3 g/L)	337 mg/L	Rat	None	35	6	↑ GSH peroxidase (liver) ↑ GSH (liver) ↑ Vitamin A (liver) ↑ Total antioxidant status (liver) ↓ MDA (liver) ↑ SOD activity (serum) ↓ GSH peroxidase (serum) ↓ MDA (serum) ↓ SOD activity (brain) ↓ GSH peroxidase (brain) ↓ MDA (brain)	SOD activity (liver) Vitamin E (liver) Vitamin C (liver) β-Carotene (liver) Vitamin E (serum) Vitamin A (serum) Vitamin C (serum) β-carotene (serum) Vitamin E (brain) Vitamin A (brain) Vitamin C (brain) β-Carotene (brain)	40
Green tea (3 g/L)	10% of green tea	Rabbit (hypercholesterolemic)		147	20	↑ Plasma vitamin A ↑ LDL vitamin E	Serum cholesterol, LDL cholesterol, and lipids Vitamins E and C Total antioxidant activity of plasma Lipids peroxidation Aortic atherosclerotic lesions	46
GTE (0.5%)	51.86% of GTE	Rat	Streptozotocin (55 mg/kg)	28	10	↓ Production of thromboxane A2 (kidney) ↑ Prostacyclin formation ↑ Glomerular filtration rate		47
GTE (0.5%)		Rat	Streptozotocin (55 mg/kg)	28	10	↓ Kidney microsomal concentration ↑ Kidney microsomal hydrolysis of phosphatidylethanolamine	Phospholipase A2 activity Production of thromboxane	48
GTE (1%, wt:wt)	45.3% of GTE	Rat	Streptozotocin (55 mg/kg)	28	10	↑ Phospholipase A2 activity ↑ Cyclooxygenase activity ↓ Concentration of platelet thromboxan B2 ↑ Aortic prostaglandin F1α		49

Ingested dose/d	EGCg eq	Species	Stress	Duration *d*	Subjects/ group	Biomarkers affected	Biomarkers not affected	Reference
GTE (20 mg/kg)		Rat	Cisplatin	40	6	↓ Blood urea nitrogen ↓ Serum creatinine ↓ Serum malondialdehyde ↓ Kidney ↓ SOD activity ↑ Catalase activity	Urinary protein excretion Urinary glucose excretion Glutathione peroxidase activity	50
GTE (100 mg/kg)		Rat	Alloxan (120 mg/kg)	15	6	↓ Serum glucose level ↓ Lipid peroxidation ↓ Level creatinine ↑ SOD		51
GTE (130 mg)		Zucker rat		10	5	↓ Body weight ↓ Liver weight ↓ Epidymal, perirenal, and mesenteric adipose weight ↓ Total plasma cholesterol ↑ Total plasma protein ↓ Liver triglycerides	Plasma triglycerides Liver total cholesterol	52
GTE (1%, wt:wt)	20.16% of extract	Rat	Sucrose-rich diet (580 g/kg diet)	25	6	↓ Plasma total triglycerides ↓ Plasma total cholesterol ↓ Liver triglycerides ↓ Heart cholesterol	HDL cholesterol Liver cholesterol Heart triglycerides	53
GTE (0.5%, wt:v)	199.49 g/kg	Rat	Oral glucose tolerance test	84	8	↓ Plasma insulin level ↓ Plasma free fatty acids level ↓ Plasma triglyceride level ↑ Glucose uptake by adipocytes	Plasma glucose level	54

[1] Abbreviations: GSH, glutathione; MDA, malonyl dialdehyde; SHRSP, spontaneously hypertensive stroke-prone.

these ions (60). Green tea catechins have the potential to affect absorption and metabolism of ions because flavonoids interact with a variety of metal ions (66).

Effects on drug-metabolizing enzymes. Long-term ingestion of green tea increases UDP-glucuronosyltransferase (UDP-GT) activity in rats (62,63,65), and after being absorbed, catechins are metabolized by drug-metabolizing enzymes in various organs (67–69). Thus, the increased glucuronidation through UDP-GT induction is postulated to contribute to the anticarcinogenic effect of green tea by facilitating the metabolism of chemical carcinogens into inactive products that are readily excreted. The interaction between 2-amino-3-methylimidazol(4,5-*f*)quinoline (IQ) and green tea catechin metabolism was examined (64). IQ is a precarcinogen that was originally detected in an extract of fried meat. The major route of IQ biotransformation in rats is cytochrome P450 in a first step, followed by conjugation to a sulfate and a glucuronide conjugate. Green tea modifies IQ metabolism in rats, increasing the formation of IQ glucuronides, which are then excreted in the urine (Table 3). Moreover, protection against cancers induced by polycyclic aromatic hydrocarbons by green tea catechins may be due to the inhibition of their cytochrome P450 (CYP) metabolism, but the effect of green tea on CYP enzymes depends on the particular form. Indeed, long-term consumption of green tea increases CYP1A1 and 1A2 activities, but not 2B1 and 2E1 activities, in normal rats (Table 3). Also, it is difficult to draw conclusions about a beneficial effect of green tea against carcinogens involving only modulation of this metabolic pathway.

Effects on hormone metabolism. At a high dose (5% of diet for 13 wk), GTE induced a thyroid enlargement (goiter) in normal rats (58,59). This high-level treatment modified the plasma concentrations of the thyroid hormones (Table 2). However, drinking even a very high dietary amount of green tea would be unlikely to cause these types of effects.

Conclusions

Studies demonstrate biological effects with ingested doses of green tea or EGCg ranging from 0.01 to 2.5% of the diet. Different preparation methods were employed: *1*) green tea was prepared with fresh leaves infused in hot water, filtered, and given to the animals as a drink; *2*) GTE was dissolved in the drinking water; *3*) GTE was mixed with the diet; and *4*) EGCg was added to the drinking water or to the diet. These preparation methods influence the catechins both quantitatively and qualitatively; the amount of catechins also varies in the original tea leaves (variety, origin, growing conditions, etc.) (70). The preparation of fresh green tea cannot totally extract catechin from the leaves; therefore, the concentration found differs from the absolute values determined through the complete extraction of leaves (71). Moreover, catechins are relatively unstable and could be quantitatively and qualitatively modified during the time frame of the experiment (72,73). Thus, comparison of ingested doses for animal studies is not possible because the catechin quantification before administration is often not known. Moreover, because drinking water or food consumption is not generally indicated, the ingested quantity per animal cannot be precisely evaluated (mg/kg metabolic wt). In consequence, the strict relation between biological effect (effect/dose) and green tea ingestion is difficult to evaluate between studies.

Generally, studies using animal models show that green tea (catechins) provide some protection against degenerative diseases. Green tea catechins could act as antitumorigenic agents and as immune modulators in immunodysfunction caused by transplanted tumors or by carcinogen treatment. Green tea has an antiproliferative activity on hepatoma cells and a hypolipidemic activity in hepatoma-treated rats, prevented hepatoxicity in some studies, and could act as a preventive agent against mammary cancer postinitiation. Long-term feeding of tea catechins could be beneficial in suppressing high-fat diet–induced obesity by modulating lipid metabolism, could have a

TABLE 3

Effects of green tea catechins on other diseases in animal models

Ingested Dose/d	EGCg equivalent	Species	Stress	Period *d*	Subjects/ group	Biomarkers affected	Biomarkers not affected	Reference
GTE (5%)	32.1% of GTE	Rat		91	10	↑ Thyroid weight ↓ Body weight Hypertrophy and/or hyperplasia of thyroid cells		58
GTE (5%, wt:wt)	32.1% of GTE	Rat		56	5	↓ Body weight ↑ Thyroid weight ↓ Prostate gland weight ↓ Testis weight ↑ Plasma thyroid stimulating hormone ↓ Plasma thyroxine ↓ Plasma triiodothyronine ↑ Plasma luteinizing hormone	Follicle-stimulating hormone	59
GTE (1%, wt:v)		Rat		42	6		Plasma iron, copper, zinc, and manganese	60
GTE (2%, wt:v)		Rat		49	8	↑ Apparent absorption rate of manganese ↑ Manganese content in tibia ↓ Calcium absorption ↓ Cerebrum calcium content ↓ Apparent absorption of zinc	Apparent absorption of copper Copper concentration in tibia	61
GTE (0.5%, wt:v)		Rat		28	8	↑ CYP 1A2 activity ↑ Glutathione-S-transferase ↑ Total IG1 ↓ Type II collagen-specific IgG	CYP 2E, 2D and 3A activity Plasma cholesterol, HDL cholesterol, and triglycerides	62
Green tea (2%, v:v)		Rat		42	4	↑ CYP 1A1 activity ↑ CYP 1A2 activity ↑ UDP-GT activity	CYP 2B1 activity CYP 2E1 activity CYP 3A4 activity Glutathione S-transferase activity Plasma GSH concentration Plasma cysteine concentration Plasma cholesterol concentration HDL cholesterol concentration Plasma triglycerides concentration Plasma testosterone concentration	63
Green tea (2%, wt:v)		Rat	2-amino-3-methylamidazoquinone	42	5	↑ 2-amino-3-methylamidazoquinone urinary excretion		64
GTE (5%, wt:v)		Rat		28		↑ Liver catalase activity ↓ Liver cytosolic protein ↑ Glutathione S-transferase activity ↑ UDP-GT activity	Epoxide hydrolase activity	65

beneficial effect against lipid and glucose metabolism disorders implicated in type 2 diabetes, and could reduce the risk of cardiovascular disease.

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