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

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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 hepatotoxicity. 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

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-methylimidazo(4,5-f)quinoline; MNNG, methyl-N′-nitro-N-nitrosoguanidine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; PGI2, prostacyclin I2; SOD, superoxide dismutase; TRAMP, transgenic adenocarcinoma of the mouse prostate; TXA2, thromboxane A2; UDP-GT, UDP-glucuronosyltransferase.

(–)-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, nonalloylated catechins are present in plasma as conjugated forms (10–12), except for EGCg and Ec, 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 vivo biological effects of the conjugates.
<table>
<thead>
<tr>
<th>Ingested dose/d</th>
<th>EGCg equivalent</th>
<th>Species</th>
<th>Stress</th>
<th>Duration</th>
<th>Subjects/group</th>
<th>Biomarkers affected</th>
<th>Biomarkers not affected</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTE (1.5%, wt/v)</td>
<td>Hamster</td>
<td>DMBA (0.5%)</td>
<td>105</td>
<td>16</td>
<td>Oral tumor burden</td>
<td>Dysplasia and oral carcinoma</td>
<td>Micronuclei formation</td>
<td>Proliferating cell nuclear antigen</td>
</tr>
<tr>
<td>GTE (6 g/L)</td>
<td>Hamster</td>
<td>DMBA (0.5%)</td>
<td>126</td>
<td>28</td>
<td>Number of oral tumors</td>
<td>Micronuclei formation</td>
<td>Proliferating cell nuclear antigen</td>
<td>15</td>
</tr>
<tr>
<td>GTE (0.1%)</td>
<td>Mouse</td>
<td>ENNG (100 mg/L)</td>
<td>84</td>
<td>Not given</td>
<td>Colon tumors</td>
<td>Colon tumors</td>
<td>Aberrant crypt foci</td>
<td>Number of tumors</td>
</tr>
<tr>
<td>GTE (0.025%)</td>
<td>Mouse</td>
<td>ENNG (100 mg/L)</td>
<td>84</td>
<td>Not given</td>
<td>Proliferating cell nuclear antigen</td>
<td>Ras-p21 and Bcl-2 expression</td>
<td>Bax expression</td>
<td>Colonic mucosal lipid</td>
</tr>
<tr>
<td>EGCg</td>
<td>Rat</td>
<td>DMH (20 mg/kg)</td>
<td>224</td>
<td>42</td>
<td>Incidence of gastric carcinogenesis; number of adenocarcinomas, adenomas, adenomatous hyperplasias</td>
<td>Volume of oral tumors</td>
<td>Squamous cell carcinoma</td>
<td>Duodenal tumors</td>
</tr>
<tr>
<td>GTE (0.01%)</td>
<td>Rat</td>
<td>AOM (7.4 mg/kg)</td>
<td>112</td>
<td>Not given</td>
<td>DNA damage</td>
<td>Number of lung tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTE (0.1%)</td>
<td>Rat</td>
<td>AOM (7.4 mg/kg)</td>
<td>112</td>
<td>Not given</td>
<td>Number of lung tumors</td>
<td>Incidence of tumors</td>
<td>Level of dysplasia</td>
<td>Cancer invasiveness</td>
</tr>
<tr>
<td>Green tea (2%, wt/v)</td>
<td>Rat</td>
<td>DMH (25 mg/kg)</td>
<td>10</td>
<td>8</td>
<td>Lung tumor weight</td>
<td>Thymus weight</td>
<td>CD8</td>
<td>24</td>
</tr>
<tr>
<td>GTE (0.5%, wt/v)</td>
<td>Rat</td>
<td>DMH (20 mg/kg)</td>
<td>112</td>
<td>15</td>
<td>Number of liver tumors</td>
<td>Number of liver tumors</td>
<td>Hepatic adenomas</td>
<td>Number of diameter for tumors</td>
</tr>
<tr>
<td>GTE (0.63%, wt/v)</td>
<td>Mouse</td>
<td>DENA (50 μg/kg)</td>
<td>280</td>
<td>15</td>
<td>Number of liver tumors</td>
<td>Hepatic adenomas</td>
<td>Number of diameter for tumors</td>
<td>Lung adenoma multiplicity</td>
</tr>
<tr>
<td>Green tea (1.25%, wt/v)</td>
<td>Mouse</td>
<td>DENA (50 μg/kg)</td>
<td>280</td>
<td>15</td>
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<td>Number of diameter for tumors</td>
<td>Lung adenoma multiplicity</td>
</tr>
</tbody>
</table>
EGCg are useful in preventing gastrointestinal carcinogenesis. Nevertheless, a study performed under similar conditions found that green tea had no effect on colorectal carcinogenesis induced by methylmethane (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 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).

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).

<table>
<thead>
<tr>
<th>Ingested dose/d</th>
<th>EGCg equivalent</th>
<th>Species</th>
<th>Stress</th>
<th>Duration (d)</th>
<th>Subjects/group</th>
<th>Biomarkers affected</th>
<th>Biomarkers not affected</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTE (0.1%, wt:v)</td>
<td>0.085%</td>
<td>Rat</td>
<td>DENA (200 mg/kg)</td>
<td>70</td>
<td>10</td>
<td>↓ Liver DNA damage during carcinogenesis</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>GTE (1%)</td>
<td>0.085%</td>
<td>Rat</td>
<td>DENA (200 mg/kg)</td>
<td>42</td>
<td>13</td>
<td>↓ Liver weight</td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>GTE (2%, wt:v)</td>
<td>0.29%</td>
<td>Rat</td>
<td>2-NP (120 mg/kg)</td>
<td>14</td>
<td>5</td>
<td>↓ Glutathione S-transferase</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>Green tea (2%, wt:v)</td>
<td>12.4%</td>
<td>Rat</td>
<td>Aflatoxin (25 mg/kg) + CCl4 (0.8 mL/kg)</td>
<td>24</td>
<td>12</td>
<td>↓ Cell proliferation in the liver</td>
<td></td>
<td>29</td>
</tr>
<tr>
<td>GTE (0.5%, wt:v)</td>
<td>0.4%</td>
<td>Rat</td>
<td>Subcutaneous injection of AH109A cells (10^6)</td>
<td>14</td>
<td>10</td>
<td>↓ Lipid peroxide levels</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>GTE (0.1%, wt:v)</td>
<td>0.085%</td>
<td>Rat</td>
<td>Choline-deficient diet</td>
<td>70</td>
<td>10</td>
<td>↓ Lactate dehydrogenase</td>
<td></td>
<td>31</td>
</tr>
<tr>
<td>GTE (0.5% of diet)</td>
<td>0.29%</td>
<td>Rat (female)</td>
<td>DMBA (50 mg/kg)</td>
<td>161</td>
<td>14</td>
<td>↓ Alanine amino transferase</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>EGCG (0.5%)</td>
<td>0.4%</td>
<td>Rat (female)</td>
<td>DMBA (50 mg/kg)</td>
<td>161</td>
<td>14</td>
<td>↓ Glutathione S-transferase (liver)</td>
<td></td>
<td>33</td>
</tr>
<tr>
<td>GTE (1%)</td>
<td>0.4%</td>
<td>Rat (female)</td>
<td>DMBA (25 mg/kg)</td>
<td>252</td>
<td>20</td>
<td>↓ Lipid peroxide level (liver)</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>EGCg (1%)</td>
<td>0.1%</td>
<td>Nude mouse</td>
<td>Transplantation RIII/MG cells (10^6)</td>
<td>140</td>
<td>3</td>
<td>↓ Fibrosis</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>GTE (0.3%, wt:v)</td>
<td>0.1%</td>
<td>Rat (female)</td>
<td>TRAMP mouse</td>
<td>119</td>
<td>15</td>
<td>↓ Body weight</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>GTE (0.1%, wt:v)</td>
<td>0.62 mg/kg</td>
<td>Rat (female)</td>
<td>TRAMP mouse</td>
<td>168</td>
<td>10</td>
<td>↓ Number of noninvasive mammary malignant tumors</td>
<td></td>
<td>37</td>
</tr>
</tbody>
</table>
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-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-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-butaneone (NNK) is generally used to induce lung tumors in mice. 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 CD8\(^+\) / CD4\(^+\) ratio. Ingestion of green tea improved immune functions and inhibited tumor growth (24).

These results show that tea catechins could act as antitumorogenic 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 hypertriglycerideremia) (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 hepatotoxicity.

**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, in one study reports that catechins 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 levels 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 A2 (TXA2) and prostacyclin I2 (PGI2) is controlled, and the balance between them is important to maintain homeostasis in vivo. A modification of the PGI2:TXA2 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 A2 (which is higher in the case of kidney disorders) and the fatty acid composition. Streptozotocin increases the synthesis of TXA2 and decreases that of PGI2. Administration of green tea catechins in rats pretreated with streptozotocin decreases the synthesis of TXA2 and increases that of PGI2 (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 antiatherogenic 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 PGI2:TXA2 ratio in rats treated with streptozotocin and also suppressed phospholipase A2 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 ion 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

<table>
<thead>
<tr>
<th>Ingested dose/d</th>
<th>EGCG eq</th>
<th>Species</th>
<th>Stress</th>
<th>Duration</th>
<th>Subjects/group</th>
<th>Biomarkers affected</th>
<th>Biomarkers not affected</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green tea (3.5 g/L)</td>
<td></td>
<td>SHRSP1 rat</td>
<td>20</td>
<td>5</td>
<td></td>
<td>Systolic and diastolic blood pressure, Catalase expression (aorta)</td>
<td>Urinary nitric oxide excretion</td>
<td>41</td>
</tr>
<tr>
<td>EGCG (1%)</td>
<td></td>
<td>Rat</td>
<td>Dietary cholesterol (5 g/kg diet)</td>
<td>24</td>
<td>8</td>
<td>Total cholesterol in plasma, Hepatic total cholesterol</td>
<td>Liver lipid concentration</td>
<td>42</td>
</tr>
<tr>
<td>GTE (0.8 g/L; 4 mL/d)</td>
<td>584 g/kg</td>
<td>Mouse Apo (E) deficiency</td>
<td></td>
<td>98</td>
<td>17</td>
<td>Total cholesterol in plasma, Hepatic total cholesterol</td>
<td>Plasma cholesterol</td>
<td>43</td>
</tr>
<tr>
<td>GTE (0.5%, wt:wt)</td>
<td>74% of catechin</td>
<td>Mouse C57BL/6 J</td>
<td>High-fat diet (300 g/kg diet)</td>
<td>308</td>
<td>5</td>
<td>Body weight, Atherosclerotic area</td>
<td>Plasma cholesterol</td>
<td>44</td>
</tr>
<tr>
<td>GTE (2.5%)</td>
<td>11.6% of GTE</td>
<td>Rat</td>
<td>Dietary cholesterol (10 g/kg diet)</td>
<td>35</td>
<td>?</td>
<td>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, LDL peroxidation, Serum antioxidant capacity, Total plasma cholesterol, Plasma free cholesterol, LDL cholesterol, HDL cholesterol, Cholesterol absorption α-Tocopherol absorption</td>
<td>SOD activity (liver), Vitamin A (liver)</td>
<td>39</td>
</tr>
<tr>
<td>GTE (120 mg)</td>
<td></td>
<td>Rat (ovariectomized)</td>
<td></td>
<td>1</td>
<td>5</td>
<td>Body weight, Atherosclerotic area</td>
<td>SOD activity (liver), Vitamin A (liver)</td>
<td>45</td>
</tr>
<tr>
<td>GTE (3 g/L)</td>
<td>337 mg/L</td>
<td>Rat</td>
<td>None</td>
<td>35</td>
<td>6</td>
<td>Body weight, Atherosclerotic area</td>
<td>SOD activity (liver), Vitamin A (liver)</td>
<td>40</td>
</tr>
<tr>
<td>Green tea (3 g/L)</td>
<td>10% of green tea</td>
<td>Rabbit (hypercholesterolemic)</td>
<td></td>
<td>147</td>
<td>20</td>
<td>Body weight, Atherosclerotic area</td>
<td>SOD activity (liver), Vitamin A (liver)</td>
<td>46</td>
</tr>
<tr>
<td>GTE (0.5%)</td>
<td>51.86% of GTE</td>
<td>Rat</td>
<td>Streptozotocin (55 mg/kg)</td>
<td>28</td>
<td>10</td>
<td>Production of thromboxane A2 (kidney), Prostacyclin formation, Glomerular filtration rate, Kidney microsomal concentration, Kidney microsomal hydrolysis of phosphatidylethanolamine, Phospholipase A2 activity, Cyclooxygenase activity, Concentration of platelet thromboxan B2, Aortic prostaglandin F1α</td>
<td>Phospholipase A2 activity, Production of thromboxane</td>
<td>47</td>
</tr>
<tr>
<td>GTE (0.5%)</td>
<td></td>
<td>Rat</td>
<td>Streptozotocin (55 mg/kg)</td>
<td>28</td>
<td>10</td>
<td>Production of thromboxane A2 (kidney), Prostacyclin formation, Glomerular filtration rate, Kidney microsomal concentration, Kidney microsomal hydrolysis of phosphatidylethanolamine, Phospholipase A2 activity, Cyclooxygenase activity, Concentration of platelet thromboxan B2, Aortic prostaglandin F1α</td>
<td>Phospholipase A2 activity, Production of thromboxane</td>
<td>48</td>
</tr>
<tr>
<td>GTE (1%, wt:wt)</td>
<td>45.3% of GTE</td>
<td>Rat</td>
<td>Streptozotocin (55 mg/kg)</td>
<td>28</td>
<td>10</td>
<td>Production of thromboxane A2 (kidney), Prostacyclin formation, Glomerular filtration rate, Kidney microsomal concentration, Kidney microsomal hydrolysis of phosphatidylethanolamine, Phospholipase A2 activity, Cyclooxygenase activity, Concentration of platelet thromboxan B2, Aortic prostaglandin F1α</td>
<td>Phospholipase A2 activity, Production of thromboxane</td>
<td>49</td>
</tr>
</tbody>
</table>
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 (UDPGT) 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 (58,59). This high-level treatment modified the metabolism 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. In consequence, the strict relation between biological effect (effect/dose) and green tea ingestion (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
beneficial effect against lipid and glucose metabolism disorders implicated in type 2 diabetes, and could reduce the risk of cardiovascular disease.

**LITERATURE CITED**


