Tea (Camellia sinensis) is the most commonly consumed prepared beverage in the world, and ranks only second to that of water for all beverages consumed.\(^1,2\) Green tea is rich in polyphenolic catechins, especially epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC; Figure 7.1). Of these, EGCG has received the most extensive study because it is thought to be primarily responsible for the health benefits of green tea. Although green tea is consumed less frequently than black tea, its popularity has increased due to growing knowledge of its health benefits. For example, epidemiological evidence supports that green tea consumption decreases the risk of cardiometabolic disorders and some forms of cancer.\(^3\)\(^{\text{-}}\)\(^{\text{15}}\) These findings have laid the foundation to define the bioactivities of green tea, with evidence indicating that catechins improve health status through antioxidant, anti-inflammatory, and metabolic benefits.
7.2 HISTORY OF GREEN TEA

The tea plant (*Camellia sinensis*) originated in China prior to spreading throughout Asia and Europe before reaching the New World by the seventeenth century. The discovery of tea is connected to the cultural history of China, with its first mention dating back nearly 5000 years ago. Although Emperor Shen Nung is credited with its discovery in 2737 BC, the first written record appeared around 400 BC in the Erh Ya, a Chinese dictionary. In 780 AD, Lu Yu authored *The Classic of Tea* to popularize tea while also providing among the earliest records of green tea processing.

Green tea was developed initially by the Chinese, who exposed the tea leaves to hot steam or heat prior to drying. Throughout Chinese history, green tea leaf preparations varied from steaming and compressing tea leaves into bricks or as powdered tea formation. Green tea became prevalent in Japan by the sixth century, coinciding with the preparation of matcha, a powdered green tea that continues to be popular. Tea production exceeds three billion kilograms annually. Of this, green tea represents ~20%–22% of global tea production, with most being consumed in Asia. However, the production of green tea is on a trajectory to outpace that of black tea due to consumer demand for healthy beverages and dietary supplements.

7.3 PROCESSING AND COMPOSITION

7.3.1 GREEN TEA PROCESSING

Green, black, and oolong teas are all derived from the leaves and buds of *Camellia sinensis*. Although each is prepared from the same plant, they differ in post-harvest processing. The leaves intended for green tea are unfermented, whereas those for black and oolong tea are fully and partially fermented, respectively. Tea leaves used for the manufacture of green tea are processed rapidly upon harvesting including high temperature exposure by steaming or pan frying prior to being rolled.
This inactivates polyphenol oxidase and peroxidases that otherwise cause oxidation (i.e., fermentation) of the catechins (Table 7.1).

### 7.3.2 Catechin Structure and Composition

The phytochemical composition of green tea is influenced by its growing conditions, including geographical location, climate, season, and leaf maturity. Catechins (flavan-3-ols; Figure 7.1) are the major polyphenols in green tea and account for ∼30%–40% of the dry weight of tea leaves. Catechins have a 2-phenyl benzopyran structure with aromatic A- and B-rings that are connected to a 3-carbon oxygenated heterocyclic C-ring. Catechins are characterized by a meta-5,7-dihydroxy substitution on the A-ring and either a di-hydroxy (EC, ECG) or tri-hydroxy (EGC, EGCG) substitution on the B-ring. EGCG and ECG also contain a gallic acid moiety that is esterified to the 3-carbon of the C-ring.

EGCG is the most abundant catechin, and can account for 50%–80% of the total catechin content of green tea. Green tea also contains low levels of catechin isomers (e.g., gallocatechin gallate), dimers (e.g., EGC-di-gallate), and methylated metabolites (e.g., 3-methyl-EC). Although the catechin content varies by commercial source and brewing technique, freshly brewed green tea has a greater amount of total catechins than both black and oolong teas, with EGCG being most abundant, followed by EGC, ECG, and EC (Table 7.1).

### 7.3.3 Flavonoids, Caffeine, and Nutrients

Catechins represent ∼70% of the total flavonoids in green tea and the remaining flavonoid content is other flavanols and polymeric flavonoids. Non-catechin flavanols include quercetin, myricetin, kaempferol, and their glycosides. Modifications of flavanols (e.g., glucosylation, rhamnosylation, rutinosylation) have also been identified in green tea. Phenolic acids (e.g., gallic and quinic acids) also provide a small proportion of the total polyphenol content of green tea. Further, small amounts of proteins, carbohydrates, lipids, vitamins, and minerals are present in green tea, with each representing <10% of the total solids. The amino acid, theanine (3% w/w), that is unique to tea is of particular interest. Not only does it influence the flavor of tea, it exhibits anti-hypertensive benefits. Caffeine is also found in green tea at levels similar to other teas derived from *Camellia sinensis* since it is unaffected by fermentation. Caffeine is typically ∼5% of the dry weight of the tea leaf and its content in brewed tea is ∼50% that of coffee. However, leaf size, brewing time, and temperature influence the caffeine content of prepared tea.

### Table 7.1

<table>
<thead>
<tr>
<th></th>
<th>Green Tea</th>
<th>Black Tea</th>
<th>Oolong Tea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epicatechin (EC)</td>
<td>20.0</td>
<td>15.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Epicatechin gallate (ECG)</td>
<td>25.2</td>
<td>12.5</td>
<td>14.7</td>
</tr>
<tr>
<td>Epigallocatechin (EGC)</td>
<td>26.8</td>
<td>6.8</td>
<td>21.8</td>
</tr>
<tr>
<td>Epigallocatechin gallate (EGCG)</td>
<td>105.0</td>
<td>14.6</td>
<td>66.2</td>
</tr>
<tr>
<td>Total Catechins</td>
<td>177.0</td>
<td>49.1</td>
<td>111.0</td>
</tr>
</tbody>
</table>


*Note:* Green tea is non-fermented, thereby preserving catechin content (mg/250 mL), whereas catechins are degraded with fermentation. Partially fermented oolong tea has less catechin content than green tea, but retains a greater proportion of catechins compared with fully fermented black tea.
7.4 GREEN TEA CATECHIN BIOAVAILABILITY

7.4.1 Catechin Absorption

The bioavailability and metabolism of green tea catechins have been studied extensively in humans and animals (Figure 7.2). Catechins are stable during the oral and gastric phases of digestion, which permits their availability for small intestinal absorption. Intestinal absorption may be transporter mediated (e.g., monocarboxylic acid transporter) or occur through passive diffusion. Regardless of the mechanism, catechin absorption is overall quite poor, although non-gallated catechins (EC, EGC) compared with gallated catechins (EGCG, ECG) appear to be better absorbed. Highlighting their poor absorption are estimates from humans indicating that only 0.2%–2.0% of EGCG and EGC is absorbed. This is attributed to the instability of catechins at the near-neutral pH of the intestines and their high rates of luminal efflux from the enterocyte that is mediated by an ATP-binding cassette transporter.

7.4.2 Catechin Metabolism

Catechins are not reported to undergo phase I cytochrome P450 metabolism (Figure 7.3). However, absorbed catechins undergo extensive phase II xenobiotic metabolism at the small intestine and liver to yield glucuronidated, sulfated, and methylated catechin metabolites. In humans, maximal plasma concentrations are 0.07–1.8 µM at ~1–3 hours post-ingestion with half-lives of ~2.5–5.7 hours. Circulating EGCG is primarily in unconjugated form whereas other catechins are frequently conjugated metabolites, which enhances their elimination. In part, the poor bioavailability of catechins is attributed to xenobiotic metabolism that is initiated at the small intestines. Catechins readily undergo glucuronidation by uridine 5'-diphosphate glucuronosyltransferases (UGTs). UGT1 is primarily responsible for catechin glucuronidation, and

![Figure 7.2](image-url)
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Incubation of EGCG and EGC in the presence of UGTs yields EGCG-4″-O-glucuronide and EGC-3′-O-glucuronide, with evidence suggesting that UGTs have preferential affinity toward EGCG compared with EGC. Following small intestinal metabolism, glucuronidated catechins enter the portal and systemic circulation and/or can be effluxed back to the intestinal lumen by multidrug-resistant proteins 1 and 2.

Small intestinal and hepatic sulfotransferases (SULTs) and catechol-O-methyltransferases (COMTs) are also involved in xenobiotic metabolism of catechins. The expression of these enzymes predominates in the liver. SULT1A1 and SULT1A3, with 3′-phosphoadenosine-5′-phosphosulfate serving as the sulfate donor, are thought to be the major isoenzymes responsible for the sulfation of catechins. Sulfation of EC is apparently favored over glucuronidation, and conjugation has been identified at the 3′- or 4′-carbon of the B ring or at the 5- or 7-carbon of the A ring. COMTs are also highly expressed in the liver, kidneys, and intestines. Like other phase II reactions, methylation increases hydrophilicity, but subsequent glucuronidation or sulfation is likely needed to facilitate metabolite elimination. It is therefore common to detect catechin metabolites having multiple phase II reaction conjugations.

Other metabolic pathways for catechins have been reported, but have received limited attention. These include glucosidation products of EGCG that are generated by UDP-glucosyltransferases have been identified in urine of mice. Further, thiol conjugates of EGCG also exist but may only form in response to supraphysiological exposures to EGCG.

### 7.4.3 Microbial Metabolism

Because catechins have poor bioavailability, much of what is ingested is directed to the distal gut where the potential exists for microbial metabolism. Indeed, the colon contains more than 100 trillion microbes with diverse capabilities for extensive and complex catechin metabolism. Microbial metabolism of catechins involves: (1) C-ring fission and hydrolysis of gallic acid from those catechins that are gallated; (2) lactonization with partial dehydroxylation of the B-ring; (3) phenolic acid formation from hydrolysis, dehydrogenation, and glycine conjugation reactions; and (4) other oxidation and conjugation reactions to form benzoic acids.

Studies in ileostomy patients have provided insights regarding microbial metabolism of catechins. In these patients, 439 μmol of catechins and their metabolites were recovered in
the ileal fluid within 24 h ingestion of a green tea beverage containing 634 µmol of catechins. This suggests that ~30% of catechins are absorbed at the small intestines, whereas the remaining ~70% is either unabsorbed, or potentially absorbed, metabolized, and subsequently excreted into the intestinal lumen prior to microbial metabolism.

Microbial metabolites of catechins that have been identified include ring fission products (e.g., valerolactones) and phenolic acids (e.g., hydroxybenzoic acids). These metabolites have been detected in plasma and urine of humans following green tea catechin ingestion. Major ring fission products include: 5-(3′,4′,5′-trihydroxyphenyl)−γ-valerolactone, 5-(3′,4′-dihydroxyphenyl)−γ-valerolactone, and 5-(3′,5′-dihydroxyphenyl)−γ-valerolactone (Figure 7.1). These metabolites are most abundant in urine, where levels reach ~4–8 µM compared with circulating levels of ~0.1–0.2 µM. Peak metabolite concentrations also occur several hours (5–48 h) later than those of parental catechins. If catechin bioavailability considers microbial metabolites, these metabolites represent 6%–39% of the ingested catechin dose.

7.5 SAFETY AND TOXICITY

The well-documented health benefits of green tea and its catechins have contributed to widespread use of dietary green tea supplements in the United States. Its popularity as a beverage and supplement has also raised concerns surrounding its safety, especially hepatotoxicity. Notable clinical signs of adverse effects associated with green tea are elevated bilirubin and/or liver enzymes. These adverse effects are uncommon in humans despite studies in animals that show hepatotoxicity at very large doses of green tea catechins. Indeed, a meta-analysis of randomized control trials indicated that hepatotoxicity relating to green tea has a 0.5% occurrence rate; most were deemed mild. A systematic review by the US Pharmacopeia also identified 34 cases of liver-related adverse events. However, many cases could not be attributed directly to green tea because most individuals were using pharmacological drugs concurrently or using supplement formulations containing multiple ingredients.

A mechanism for the toxic effects of green tea is not well established. Hepatotoxicity is thought to be attributed to EGCG because of its abundance in green tea and high concentrations typically used in dietary supplements. Rodent studies have suggested that high-dose EGCG induces hepatotoxicity through a pro-oxidant mechanism. However, EGCG is absorbed limitedly, suggesting that hepatotoxicity in humans is unlikely when consumed at physiologically relevant doses. Green tea ingestion in the fasted state compared with the fed state increases plasma EGCG by ~3.5 times, suggesting that adverse effects may be alleviated if catechins are co-ingested with food. Concurrent ingestion of green tea may also interfere with prescription drug metabolism to induce a hepatotoxicity.

There are few or no adverse effects when 800 mg EGCG (~10 times the amount in a serving of freshly brewed green tea) is ingested on a single occasion or chronically. Further, no significant adverse effects were reported when EGCG (800 mg/day) was ingested for up to 1 year in overweight men, post-menopausal women, or persons with type 2 diabetes. The available evidence therefore supports that green tea is safe when consumed as recommended.

7.6 BIOACTIVITY OF CATECHINS

Extensive study has focused on the antioxidant function of catechins because of their multiple hydroxyl groups that are capable of redox reactions. Catechins are able to directly scavenge reactive oxygen/nitrogen species (e.g., superoxide radical, peroxyl radicals) and prevent downstream oxidative damage in vitro. They are also effective chelators that prevent iron- and copper-induced free radical generation. Catechins also exhibit indirect antioxidant activities by inducing host antioxidant enzymes, such as glutathione peroxidase and superoxide dismutase. Notably, though, green tea catechins likely protect against oxidative damage independent of Nrf2 signaling that upregulates cytoprotective antioxidant defenses. On the other hand, pro-oxidant activities of catechins, at least

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under \textit{in vitro} conditions, modulate cellular signaling that may help to prevent cancer.\textsuperscript{82,87} Green tea catechins also exhibit anti-inflammatory activities. Studies in preclinical models show that EGCG prevents the nuclear translocation of nuclear factor \(\kappa\)B, a pro-inflammatory transcription factor, by limiting I\(\kappa\)B phosphorylation\textsuperscript{84,88} and DNA binding activity.\textsuperscript{89} Green tea catechins also decrease pro-inflammatory responses under the transcription control of activator protein-1 by inhibiting phosphorylation of upstream kinases (i.e., extracellular signal-related protein kinases and c-jun kinases).\textsuperscript{90} However, the benefits of green tea or its catechins on inflammation have been less clear, with outcomes of some studies showing a favorable benefit and others showing a neutral effect.\textsuperscript{91–94}

### 7.7 BENEFITS OF GREEN TEA FOR CHRONIC DISEASE PREVENTION

The putative antioxidant and anti-inflammatory activities of green tea catechins have been investigated for their role to enhance metabolic function, especially in relation to obesity, cardiometabolic risk, and cancer. Several meta-analyses have examined the beneficial effects of green tea consumption on diabetes, liver diseases, and cancers (Table 7.2), whereas studies in preclinical models typically use purified catechins or green tea extract (GTE) that is enriched in catechins. In the below sections, a summary of preclinical and clinical studies is presented to provide foundational knowledge that continues to support research into the human health benefits of green tea and its catechins.

#### 7.7.1 OBESITY

Obesity is already at epidemic proportions and is expected to worsen consistent with estimates indicating that >50\% of the population worldwide will be obese by 2030.\textsuperscript{95} Evidence suggests that green tea or its catechins may help to alleviate obesity through gut-level mechanisms that limit dietary lipid absorption; peripheral effects that upregulate energy expenditure, inhibit adipogenesis, and stimulate lipid oxidation; or through satiating benefits that limit energy intake.\textsuperscript{96}

In obese adults participating in a 12-wk exercise program, the daily consumption of green tea (625 mg catechins) decreased abdominal adipose mass by 7.7\% and subcutaneous adipose mass by 8.7\% while also decreasing circulating triglyceride concentrations compared with those not receiving green tea.\textsuperscript{97} Similarly, GTE supplementation in exercising mice fed a high-fat diet

<table>
<thead>
<tr>
<th>Major Study Outcomes</th>
<th>Studies</th>
<th>Pooled Subjects</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green tea consumption is associated with lower fasting glucose, HbA1c levels, and fasting insulin</td>
<td>17</td>
<td>1133</td>
<td>108</td>
</tr>
<tr>
<td>Green tea consumption is associated with a reduced risk of liver diseases (hepatocellular carcinoma, steatosis, hepatitis, cirrhosis)</td>
<td>15</td>
<td>826,149</td>
<td>161</td>
</tr>
<tr>
<td>Green tea consumption is associated with lower plasma total cholesterol and LDL-C in obese subjects</td>
<td>21</td>
<td>1704</td>
<td>138</td>
</tr>
<tr>
<td>Green tea consumption is associated with a reduced risk for cardiovascular disease, intracerebral hemorrhage, and cerebral infarction</td>
<td>9</td>
<td>259,267</td>
<td>125</td>
</tr>
<tr>
<td>Green tea consumption is associated with lower systolic and diastolic blood pressure</td>
<td>13</td>
<td>1367</td>
<td>162</td>
</tr>
<tr>
<td>Green tea consumption is associated with a lower risk of coronary artery disease</td>
<td>5</td>
<td>53,586</td>
<td>163</td>
</tr>
<tr>
<td>Green tea consumption is associated with a reduced risk of liver cancer, especially among women</td>
<td>9</td>
<td>468,968</td>
<td>163</td>
</tr>
<tr>
<td>Green tea consumption is associated with a lower risk of lung cancer</td>
<td>12</td>
<td>107,537</td>
<td>10</td>
</tr>
<tr>
<td>Green tea consumption is associated with a lower risk of prostate cancer</td>
<td>10</td>
<td>96,511</td>
<td>164</td>
</tr>
</tbody>
</table>
significantly reduced body mass and adiposity compared with exercise or GTE supplementation alone. In overweight and obese persons, 12-wk supplementation with GTE containing EGCG (90 mg) and caffeine (50 mg) increased energy expenditure while also decreasing body mass and waist circumference. This is potentially attributed to GTE stimulating thermogenesis by increasing the release of noradrenaline that mediates non-shivering energy expenditure. Others suggest that GTE increases thermogenesis due to catechins that inhibit the activity of catechol-O-methyltransferase that otherwise degrades norepinephrine. In support, an intervention in obese Thai adults demonstrated that GTE supplementation decreased body mass and increased resting energy expenditure and the respiratory quotient. Potentially, the benefits of GTE to reduce obesity risk are attributed to effects on adipokines. For example, a double-blind, placebo-controlled trial in Taiwanese women demonstrated that GTE supplementation improved dyslipidemia while increasing circulating adiponectin concentrations; the latter were inversely related to body mass. An emergent investigative area is the study of chronic “low-grade” inflammation in relation to obesity risk. Chronic supplementation of GTE to mice fed a high-fat lowered adipose expression of the inflammatory parameters TNF-α and IL-10 and decreased body mass in association with increased circulating adiponectin concentrations and an upregulation of the lipolytic pathway.

### 7.7.2 Diabetes

Numerous studies support that GTE inhibits the progression of diabetes and related metabolic complications (e.g., insulin resistance, hyperglycemia, hepatic nephropathy, glycemic hepatotoxicity). Indeed, epidemiological studies have suggested that chronic green tea consumption is strongly correlated with a lower risk of diabetes, and controlled studies in obese mice indicate benefits of green tea to reduce circulating glucose and improve insulin sensitivity. In a meta-analysis of 17 clinical trials (n = 1133 subjects), the consumption of green tea for 2–6 months was associated with lower blood glucose, lower insulin, and lower levels of HbA1c.

In normoglycemic humans, acute supplementation of GTE limited glycemic excursions otherwise induced by a 75 g oral glucose tolerance test. Studies in rodents have suggested that the glucose-lowering activity of GTE may be attributed gallated catechins (i.e., EGCG and ECG) that limit intestinal absorption of glucose by interacting with glucose transporters. Others have suggested that GTE may reduce glycemic excursions otherwise induced by starch ingestion by inhibiting the activities of α-amylase and α-glucosidase. Further study in vitro has provided evidence that catechins inhibit pancreatic α-amylase in a non-competitive manner to prevent starch digestion and that EGCG most strongly inhibits α-glucosidase activity compared with other catechins.

In Taiwanese persons with type 2 diabetes mellitus, decaffeinated green tea three times daily for 18 weeks lowered circulating triglyceride concentrations along with insulin resistance. Further, circulating glucagon-like peptide-1 was significantly increased, which is important for regulating circulating glucose. Green tea has also been shown to manage the risk of diabetic nephropathy. Consumption of green tea polyphenols for 12 weeks lowered albuminuria, which was suggested to be improved by reducing podocyte apoptosis by activating the WNT pathway. Similar benefits also occurred in rats in which EGCG supplementation prevented nephropathy as evidenced by reduced renal fibrosis, mesangial cell hyperplasia, and improved morphometry of Bowman’s capsules within the renal system.

### 7.7.3 Nonalcoholic Fatty Liver Disease

Nonalcoholic steatohepatitis (NASH) is an early stage of nonalcoholic fatty liver disease (NAFLD) that is regarded as the hepatic manifestation of metabolic syndrome and significantly increases the risk for more progressive disorders including fibrosis, cirrhosis, and potentially hepatocellular carcinoma (HCC). Of concern is that NASH afflicts >70 million Americans, and its multifaceted etiology that is characterized by inflammation, oxidative distress, and dysregulated lipid and glucose metabolism makes it difficult to manage.
Epidemiological evidence from Japan suggested that the daily consumption of >10 cups of green tea is associated with reduced levels of liver injury (i.e., alanine and aspartate aminotransferase; ALT and AST), circulating ferritin, triglyceride, total cholesterol, LDL-C, and increased HDL-C.\(^\text{117}\) Although there are no non-invasive diagnostic measures of NASH, elevations in ALT and AST are commonly observed in these persons. No large-scale clinical trials have examined green tea to manage NASH. However, findings of a double-blind, placebo-controlled trial (n = 80 patients) indicated that GTE supplementation for 3 months lowered serum ALT, AST, and alkaline phosphatase (ALP), but ALT and ALP and not AST were similarly lowered among those allocated to placebo.\(^\text{118}\) In a separate trial (n = 17 NAFLD patients), a higher dose of catechins was reported to decrease serum ALT and urinary isoprostanes to a greater extent than a lower dose of catechins or placebo.\(^\text{119}\) These observations require further confirmation, but their promise has been well established by studies in rodent models of NASH.

In genetically obese, leptin-deficient mice, dietary GTE supplementation inhibited histological evidence of liver steatosis and reduced hepatic triglyceride levels without affecting hepatic antioxidants or circulating adiponectin.\(^\text{120}\) These benefits were likely attributed to GTE limiting adipose lipogenesis and the flux of free fatty acids to the liver, where they get esterified and stored as triglyceride.\(^\text{85}\) Separate studies in leptin-adequate rodents also indicate that GTE prevents or treats diet-induced NASH (Figure 7.4).\(^\text{121,122}\) Although early findings suggested that GTE protects against liver injury by upregulating Nrf2-dependent antioxidant defenses,\(^\text{85}\) studies in Nrf2-deficient mice...
clearly showed that GTE provides extensive Nrf2-independent hepatoprotection during NASH. Follow-up studies in rodents fed a high-fat diet suggested that GTE alleviates NASH by inhibiting NFκB activation by downregulating signaling from the pro-inflammatory receptors tumor necrosis factor receptor-1 (TNFR1) and Toll-like receptor-4 (TLR4). When studies were conducted in mice lacking intact TLR4 signaling, GTE was shown to protect against NASH in wild-type mice to the extent observed in TLR4 mutant mice that were fully protected from NASH. This suggested that GTE-mediated inhibition of TLR4/NFκB limits the induction of TNFα that is otherwise needed to induce TNFR1 signaling. The importance of limiting TLR4 signaling was further supported by studies in mice with NASH. Indeed, GTE decreased serum endotoxin (i.e., the ligand for TLR4) in association with improving intestinal integrity and mRNA expression of tight junctions. Thus, at least in rodents, GTE protects against NASH by limiting gut-derived endotoxin translocation to the liver, where it would activate TLR4/NFκB inflammation that induces hepatocellular injury. Future, well-controlled studies are needed to translate these pre-clinical findings to improve the health of humans with or at-risk of developing NASH.

### 7.7.4 Cardiovascular Disease

Cardioprotective benefits of green tea were supported by findings of a large meta-analysis ($n = 259,267$ individuals) indicating that daily consumption lowers the risk of cardiovascular disease, intracerebral hemorrhage, and cerebral infarction. Separate findings from an observational study ($n = 8552$ adults) also suggested a lower risk of cardiovascular-related morbidity among those consuming high levels of green tea.

The benefits of green tea on cardiovascular risk may be attributed to its vasoprotective activity that was observed in coronary artery disease patients who received dietary EGCG supplementation. Similar benefits on vascular function were also observed among healthy persons who were supplemented with EC. Smokers who were instructed to consume green tea daily also had lower levels of C-reactive protein and oxidized LDL in association with reduced concentrations of the platelet activation marker P-selectin. These findings suggest that the anti-inflammatory activities of green tea or its catechins help to improve vascular endothelial function. Invasive studies in rodents have also revealed that EGCG increases the activation of endothelial nitric oxide synthase, which is critical for nitric oxide–dependent vascular function. Anti-inflammatory activities of catechins that decrease the expression of cellular adhesion molecules and the recruitment of monocytes are also likely to improve vascular health. Related activities, including inhibiting matrix metalloproteinase and increasing endothelial prostacyclin production, may also contribute to the benefits of green tea to maintain vascular function.

It has also been proposed that the antioxidant activities of catechins that reduce the accumulation of reactive oxygen species and reactive nitrogen species (RNS) may also lower cardiovascular risk. For instance, intraperitoneal administration of EGCG in hypercholesterolemic mice upregulated the expression of cytoprotective genes that detoxify reactive species while also attenuating atherosclerotic plaque accumulation. Consistent with LDL oxidation being an early mediator of atherosclerosis, green catechins were reported to prevent copper-induced oxidation of LDL in vitro with the following potencies: EGCG > ECG > EC > EGC. These effects are potentially due to the metal chelating function of catechins. Whether this chelator function helps to lower cardiovascular risk in humans remains unclear, however, because catechins have poor bioavailability and concentrations studied under in vitro conditions are often at levels difficult to achieve in humans through normal consumption.

Lipid-lowering activities of green tea catechins are also likely to manage the risk of cardiovascular disease. A meta-analysis of 21 studies involving 1704 overweight and obese subjects established that green tea consumption lowered total cholesterol by 3.38 mg/dL and LDL-C by 5.29 mg/dL without affecting circulating triglyceride or HDL-C. Although the authors indicate that more high-quality and large-scale trials are needed to confirm this effect, the findings are of potential...
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importance because a lowering of circulating cholesterol by 1% reduces cardiovascular disease risk by 2%. The mechanism by which green tea lowers cholesterol is not fully defined, but may involve catechins interfering with the emulsification, digestion, and micellar solubilization of dietary fat and cholesterol or the downregulation of genes involved in lipogenesis and cholesterol biosynthesis.

7.7.5 Cancer

Lifestyle modification, especially dietary approaches, continues to be a leading recommendation for cancer chemoprevention. Although green tea has been examined for its potential benefits in reducing cancer risk, controlled trials in humans are lacking, thereby placing reliance on findings from rodent and cellular model systems. In the below sections, evidence concerning green tea or its catechins on the risk of various cancers will be summarized.

7.7.5.1 Prostate Cancer

The incidence of prostate cancer in Asian countries where green tea is widely consumed is lower than that in the United States. A study from China in patients with histologically confirmed prostate adenocarcinoma and healthy persons suggested that prostate cancer risk was inversely related to the frequency of green tea consumption and especially lower among those drinking >3 cups per day. In a cohort from Japan, findings from 49,920 middle-aged men suggested that the regular consumption of >5 cups of green tea was also associated with lower prostate cancer risk. Studies in transgenic mice that spontaneously develop metastatic prostate cancer have demonstrated that dietary supplementation with green tea polyphenols increases survival and dramatically inhibits prostate cancer incidence. The anti-tumor benefit may be due to green tea polyphenols lowering insulin-like growth factor-I and cellular proliferation. Studies in androgen-sensitive and -insensitive prostate cancer cells also support that EGCG upregulates apoptosis. Others have also reported in a human prostate cancer cell line that ECG has greater activity than other catechins to induce apoptosis by upregulating mitochondrial depolarization and increasing intracellular ROS.

7.7.5.2 Breast Cancer

The association between green tea consumption and the prevalence, recurrence, and risk of breast cancer has received study. A meta-analysis supported that the consumption of green tea consumption was inversely associated with both the recurrence and overall risk of breast cancer. These benefits may be explained by findings supporting that the regular consumption of green tea is associated with lower serum estrogen levels. This association also persistent regardless of catechol-O-methyltransferase genotype. In the MCF-7 breast cancer cell line, EGCG decreased matrix metalloproteinase by interfering with the transmembrane receptor integrin, and also reduced vascular endothelial growth factor and NFκB activation. EGCG also inhibits the aggressive growth and invasion of tamoxifen-resistant MCF-7 breast carcinoma cells by limiting epidermal growth factor receptor signaling.

7.7.5.3 Hepatocellular Carcinoma

The incidence of hepatocellular carcinoma has been largely attributed to viral infections and alcohol abuse. However, concern now exists for NAFLD because of its mediating effects on liver cancer risk that are expected to outpace those due to other historical risk factors. Individuals consuming green tea for >30 years had a lower risk of developing HCC. Liver cancer risk was also inversely related to green tea consumption among 41,761 Japanese persons who were followed for 9 years. It is thought that the antioxidant and anti-inflammatory activities of green tea catechins are responsible for these beneficial effects at the liver – both through metabolic effects and altering signal transduction pathways. For example, EGCG inhibits insulin-like growth factors and induces apoptosis in HCC cells and inhibits hepatocarcinoma cell proliferation by attenuating vascular endothelial growth factor. EGCG also attenuates platelet-derived growth factor-induced cellular proliferation and collagen expression in...
hepatic stellate cells.\textsuperscript{155} This is of importance because liver fibrosis provokes the risk toward HCC. In genetically obese mice exposed to a liver carcinogen, EGCG limited tumorigenesis in association with attenuating several pro-oncogenic pathways (e.g., signal transducer and activator of transcription-3; extracellular signal-regulated kinase; c-Jun NH(2)-terminal kinase). Further, these were also associated with lower levels of pro-inflammatory mediators (TNFα, IL-1B, IL-6, IL-18) and liver steatosis. This suggests that the early management of NASH may help to alleviate HCC risk, but controlled trials in humans are needed before clear recommendations can be established.

### 7.7.5.4 Other Cancers

Cancers at other sites have also received study in relation to green tea consumption patterns, but to a lesser extent and with somewhat equivocal outcomes. Findings of a meta-analysis, which was composed of 13 observational studies, suggested an inverse association between green tea consumption and stomach cancer in case-control studies but not in cohort studies.\textsuperscript{156} The risk of esophageal cancer was also lower among Chinese women but not men who consumed higher levels of green tea.\textsuperscript{157} Interestingly, a benefit was observed in both men and women when data were stratified to consider only nonsmokers and non-users of alcohol. Other prospective observational studies (n = 69,710 Chinese women) also suggest a lower risk of colorectal cancers among those who are regular green tea consumers.\textsuperscript{158} Paradoxically, one cohort study (n 102,137; 11 y) from Japan observed no significant association between green tea consumption and pancreatic cancer, whereas another population-based case-control study from China (n = 931 colon, 884 rectal, and 451 pancreatic cancer cases vs. 1552 healthy controls) observed an inverse relation with increased green tea use.\textsuperscript{159,160}

### 7.8 CONCLUSION

Originally consumed for its recreational pleasures, green tea has gained significant interest for its health benefits that are mediated through its polyphenolic catechins. Indeed, green tea is one of few foods rich these compounds, which is evident by the considerably lower levels present in black and oolong teas that are derived from the same tea plant. Greater study of the bioavailability and metabolism of catechins, especially those processes mediated by the gut microbiota, are expected to help define the mechanism of action of these health-promoting compounds. In addition, large-scale randomized controlled trials are needed to confirm the cardiometabolic and anti-cancer benefits observed in preclinical models and observational studies. Likewise, although green tea appears to be safe when consumed at reasonable levels, more study is needed to fully establish its safety and upper limits of recommended consumption, and to identify why certain persons may be susceptible to the rarely observed mild adverse effects.

### REFERENCES

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