

## Medicinal Benefits of Green Tea: Part I. Review of Noncancer Health Benefits

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### ABSTRACT

Tea, in the form of green or black tea, is one of the most widely consumed beverages in the world. Extracts of tea leaves also are sold as dietary supplements. However, with the increasing interest in the health properties of tea and a significant rise in scientific investigation, this review covers recent findings on the medicinal properties and noncancer health benefits of both green and black tea. In Part II, a review of anticancer properties of green tea extracts is presented. Green tea contains a unique set of catechins that possess biological activity in antioxidant, anti-angiogenesis, and antiproliferative assays potentially relevant to the prevention and treatment of various forms of cancer. Although there has been much focus on the biological properties of the major tea catechin epigallocatechin gallate (EGCg) and its antitumor properties, tea offers other health benefits; some due to the presence of other important constituents. Characteristics unrelated to the antioxidant properties of green and black teas may be responsible for tea's anticancer activity and improvement in cardiac health and atherosclerosis. Theanine in green tea may play a role in reducing stress. Oxidized catechins (theaflavins in black tea) may reduce cholesterol levels in blood. Synergistic properties of green tea extracts with other sources of polyphenolic constituents are increasingly recognized as being potentially important to the medicinal benefits of black and green teas. Furthermore, due to presumed antioxidant and antiaging properties, tea is now finding its way into topical preparations. Each of these aspects is surveyed.

### INTRODUCTION

Tea is generally consumed in the form of black, oolong, or green tea; which are all preparations originating from *Camellia sinensis*, a small plant grown mainly in China and southeast Asia. Tea is cultivated in approximately 30 countries worldwide and is consumed globally. Although the level of tea consumption varies around the world, it is believed to be second only to water.<sup>1</sup> Black tea is consumed predominantly in Western and some Asian countries and green tea is consumed predominantly in China, Japan, India, and a number of countries in north Africa and the Middle East.<sup>1</sup>

Tea originated in southwest China 5000 years ago and was originally used as a medicine for various illnesses as a

bitter concoction suggesting that the young leaves rich in catechins were used.<sup>2</sup> It is thought that at first tea leaves were used by rolling them with a milk product into cheese-like balls that would temper their somewhat bitter taste. As the boiling of water became widespread, drinking tea became normal practice. Tea was drunk from wooden bowls and the water boiled in terracotta vessels. The tea was stored in the form of powder, leaves, and cakes. Small pieces would be broken off the cakes and steeped in water.

Traditional Chinese Medicine (TCM) stresses prevention and drinking tea was recommended to healthy people between 1100 BC and 200 BC.<sup>3</sup> It was not until the T'ang dynasty (618–907 AD) that tea, long appreciated for its medicinal properties, became an object of veneration and the tea trade inside China flourished. Subsequently, drink-

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ing tea has been regarded in Asia as a generally healthful practice.

Because successful tea cultivation requires moist humid climates, the slopes of northern India, Sri Lanka, Tibet, and southern China provide some of the ideal growing areas.<sup>4</sup>

Green tea is sold as fresh or dried unfermented leaves. A highly prized collection comes from picking the very early shoots, which are almost white in color and much sought after. Tea flush is the term for these young shoots, consisting of a terminal bud and two adjacent leaves. Total polyphenols in these early shoots comprise 20% to 35% by weight, 60–80% of which are catechins. Green tea processing leads to a concentration of ~15%, but the major differences in cultivation practices for *Camellia sinensis*—harvest season, age of the leaf (plucking position), climate, environmental stress, horticulture practices, processing, and storage—are directed at producing drinking teas.<sup>5,6</sup>

The preparation of black tea requires “fermentation.” As the fresh leaves are allowed to wither and are crushed, a natural oxidative process takes place, resulting in the formation of higher molecular weight condensed polyphenolic constituents, giving black tea a stronger, more tannic flavor (Fig. 1). A less extensive, incomplete fermentation generally leads to a lighter flavored tea, popular in certain parts of Asia, known as oolong tea. Table 1 shows typical levels of the major phenolic constituents found in green and black teas. During fermentation, catechins in green tea are partially converted to theaflavins.

There are many excellent references covering the chemical constituents of tea and its pharmacological properties.<sup>7,8</sup> Scientists have identified many of the natural substances in green tea that may provide the majority of its health benefits. The major polyphenol belonging to the family of catechins and found in green tea is (-)-epigallocatechin gallate (EGCg), with lesser amounts of catechin (C), epicatechin (EC), gallic catechin (GC), gallic catechin gallate (GCG), epigallocatechin (EGC), and epicatechin gallate (ECG) (Fig. 2). In addition, caffeine, theanine, theaflavins, theobromine, theophylline, and phenolic acids such as gallic acid are

TABLE 1. TYPICAL LEVELS OF CONSTITUENTS FOUND IN BLACK AND GREEN TEA

Compound	Green tea (cup)	Black tea (cup)
Catechins	60–125 mg	30–60 mg
Theaflavins	—	3.0–6.0 mg
Caffeine	20–50 mg	30–60 mg
L-theanine	20–40 mg	20–40 mg

present in smaller quantities.<sup>9</sup> Chemical analyses and analytical methods, mostly using high performance liquid chromatometry (HPLC) and liquid chromatography-mass spectrometry (LC-MS) techniques, are now widely available for detection of these catechins.<sup>9</sup> There has been considerable interest in the breakdown products in the human body, leading to chemical studies of the metabolites of polyphenolic content in green tea extracts based on extensive HPLC analyses. A complete separation of these major constituents has been achieved (Cooper and Zhang 2004, unpublished results (Fig. 3). Quality control is improving, and standardization of the ratio and variation of the catechins in commercially available green tea extracts is leading to the availability of consistently prepared material. Because these standardized preparations will in turn be used in clinical study, there will be more confidence in the results of any future clinical evaluations.

### Weight loss

Recent studies have suggested a role for catechins in promoting weight loss.<sup>10</sup> In an animal study,<sup>11</sup> the antiobesity effect of green tea was evaluated by feeding different levels of green tea (from 1% to 4% of their diets) to female mice for 4 months. The results showed that the mice fed green tea in their diets had a significant suppression of food intake, body weight gain, and fat tissue accumulation. In addition, levels of cholesterol and triglycerides were lower. Perhaps the most interesting finding from this study was that serum leptin levels showed a decrease, indicating that green tea may have a direct beneficial effect leading to weight loss.

In some studies, green tea is associated with a mild increase in thermogenesis (increased caloric expenditure), which is generally attributed to its caffeine content.<sup>12,13</sup> At least one study has shown that green tea extract stimulates thermogenesis to an extent that is much greater than can be attributed to its caffeine content, meaning that the thermogenic properties of green tea may be due to an interaction between its high content of catechin polyphenols with caffeine. A probable theory for the thermogenic effect of green tea is an increase in levels of norepinephrine, because catechin polyphenols are known to inhibit catechol-o-methyltransferase, the enzyme that degrades norepinephrine. A randomized, placebo-controlled study of 10 individuals was conducted to investigate whether a green tea extract could

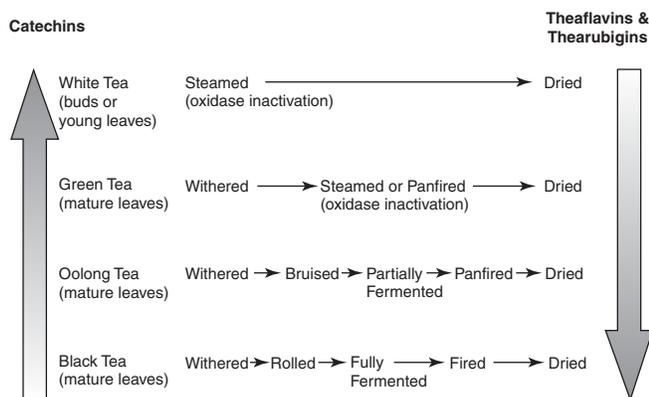


FIG. 1. Schematic of the tea extraction processes.

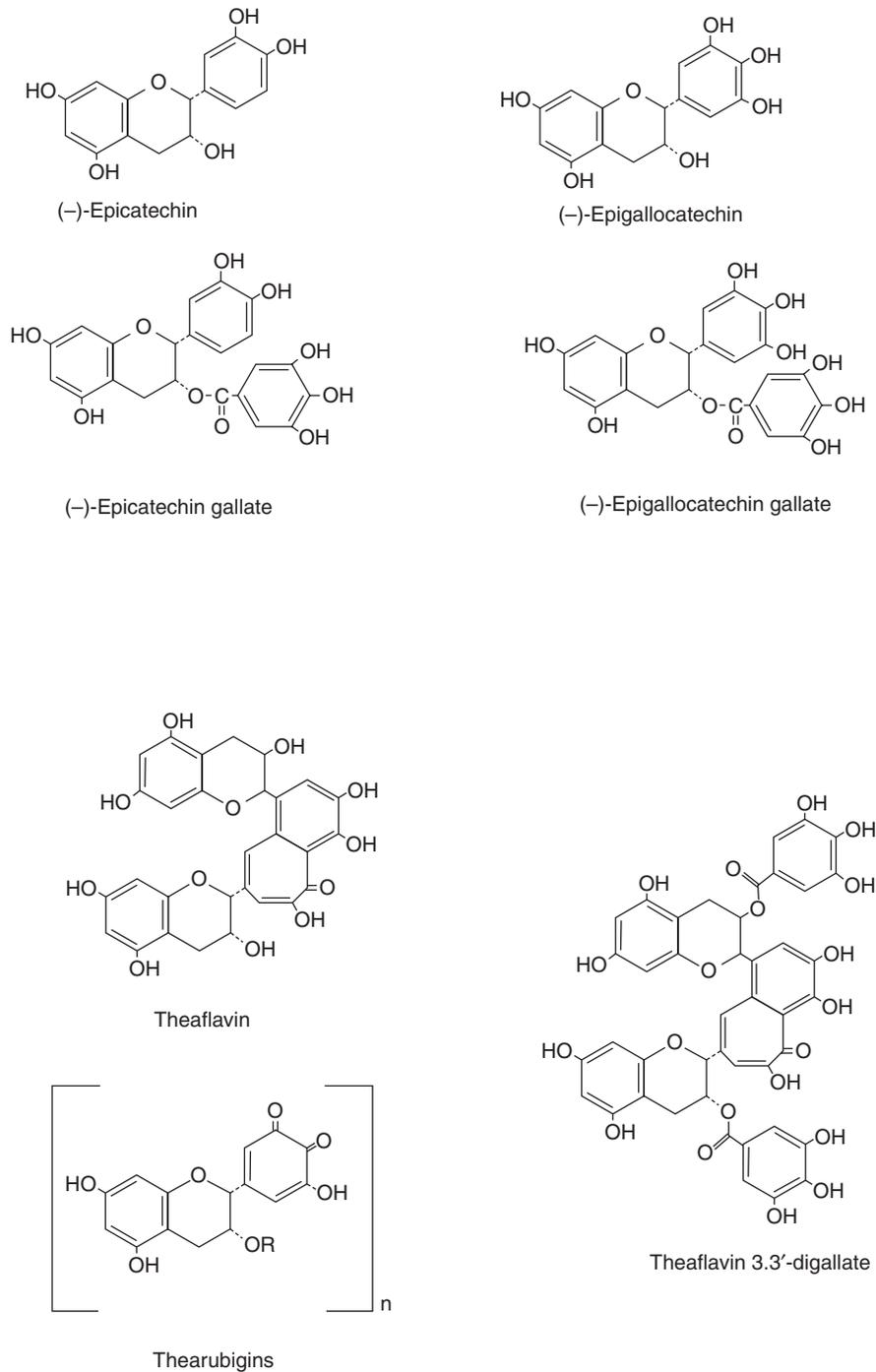
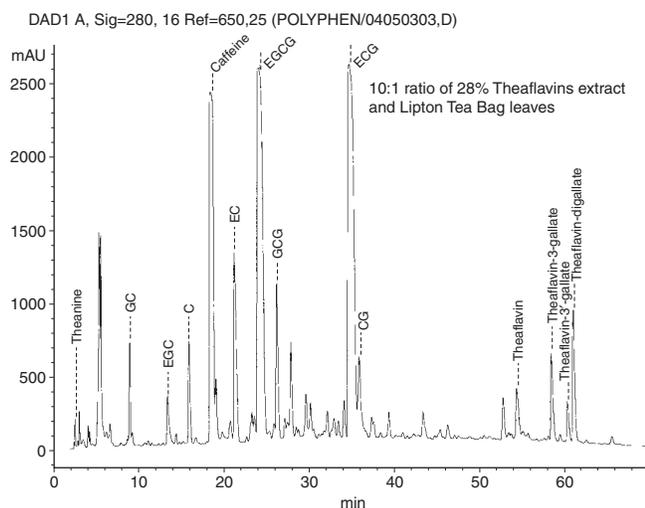


FIG. 2. Chemical structures of tea constituents.

increase energy expenditure and fat oxidation in humans over 24 hours.<sup>12</sup> Compared to placebo, the green tea extract resulted in a significant (4%) increase in energy expenditure ( $p < 0.01$ ) and a significant decrease in respiratory quotient with no change in urinary nitrogen. Twenty-four-hour urinary excretion of norepinephrine was higher during treatment with the green tea extract than with placebo. Treatment with caffeine in amounts equivalent to those found in

the green tea extract (50 mg) had no effect on energy expenditure or fat oxidation, suggesting that the thermogenic properties of green tea are due to compounds other than its caffeine content alone.

These studies on the thermogenic properties of green tea extract have demonstrated a synergistic interaction between caffeine and catechin polyphenols that appears to prolong sympathetic stimulation of thermogenesis.<sup>12,13</sup> Treatment



**FIG. 3.** High performance liquid chromatography profile of major constituents found in green and black teas.

with caffeine alone in amounts equivalent to those found in the green tea extract had no effect on energy expenditure and respiratory quotient or on urinary nitrogen or catecholamine excretion. The authors concluded that green tea has thermogenic properties and promotes fat oxidation beyond that explained by its caffeine content, with the green tea extract having a role in the control of body composition via sympathetic activation of thermogenesis, fat oxidation, or both. The green tea extract may stimulate brown adipose tissue thermogenesis to an extent which is much greater than can be attributed to its caffeine content, with thermogenic properties residing primarily in an interaction between its catechin polyphenol and caffeine content with sympathetically released noradrenaline.<sup>13</sup>

### Cardiac health and theaflavins

Green and black teas are sources of bioactive flavonoids with antioxidant activity.<sup>14</sup> The fermentation process used to prepare black tea converts many of the simpler catechin flavonoids in green tea leaves to more complex phenolic constituents such as theaflavins.<sup>15</sup> Experimentally, some catechins have been shown to inhibit a key enzyme (squalene epoxidase) in the pathway of cholesterol biosynthesis.<sup>16</sup> Theaflavin was found to be twice as effective in blocking the activity of this enzyme.<sup>17</sup> Unlike hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitors, black tea flavonoids do not interrupt the synthesis of CoQ10. In animals, catechins reduce the solubility of cholesterol in micelles—an action consistent with the observation that high doses of tea modulate cholesterol levels in animals fed high cholesterol or sugar diets.<sup>18–20</sup>

Tea consumption has been associated with decreased car-

diovascular risk. While epidemiologic studies suggest that drinking multiple cups of tea per day lowers low-density lipoprotein (LDL) cholesterol, previous trials of tea drinking and administration of green tea extract have failed to show any impact on lipids and lipoproteins in humans. Maron et al. studied the impact of a theaflavin-enriched green tea extract on the lipids and lipoproteins of subjects with mild to moderate hypercholesterolemia.<sup>21</sup> A total of 240 men and women 18 years or older on a low-fat diet with mild to moderate hypercholesterolemia were randomly assigned to receive a daily capsule containing theaflavin-enriched green tea extract (375 mg) or placebo for 12 weeks. Each active capsule contained 75 mg of theaflavins, 150 mg of green tea catechins, and 150 mg of other tea polyphenols. The extract was produced from raw *Camellia sinensis* leaves through a controlled fermentation process in which catechins were dimerized to form theaflavins. The main outcome measures were mean % changes in total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL), and triglyceride levels compared with baseline. The theaflavin-enriched green tea extract was shown to be an effective adjunct to a low-saturated-fat diet to reduce LDL in hypercholesterolemic adults and was well tolerated.<sup>21</sup>

A study<sup>22</sup> that followed 8522 Japanese men and women over a period of 12 years found that men who drank 10 cups (~32 ounces) of green tea daily had a 58% reduced risk of death from coronary heart disease compared to those who drank 3 cups a day (~10 ounces) or less. A Dutch study over 6 years of 4807 men and women showed that those who drank more than 3 cups (~13 ounces/day) of black tea had a 68% reduced risk of myocardial infarction over nontea drinkers. In a study of 552<sup>23</sup> elderly Dutch men over a period of 15 years, the risk of stroke for those who drank more than 4.7 cups/day (~20 ounces/day) of black tea was only 31% that of men who drank less than 2.6 cups/day (~11 ounces/day).

Acute ingestion of both teas has been shown to inhibit LDL oxidation in human volunteers.<sup>24</sup> Regular, frequent consumption of tea (3 or more cups daily) may reduce the risk of heart attack, according to a recent meta-analysis.<sup>25</sup> Some studies, though not all, link lower risk of heart disease with drinking large amounts of tea compared to little or none.<sup>26,27</sup>

Hong et al.<sup>28</sup> examined the effects of green tea extract on cyclo-oxygenase (COX) and lipoxygenase (LOX)-dependent arachidonic acid metabolism. Normal human colon mucosa and colon tumor tissues were investigated. At doses of 30  $\mu\text{g}/\text{mL}$ , EGCg, EGC, and ECG from green tea and theaflavins from black tea inhibited LOX-dependent activity by 30% to 75%. Inhibitory effects on COX were less pronounced.

Geleijnse et al.<sup>23</sup> investigated the association of tea and flavonoid intake with incident myocardial infarction in a Dutch population. Data were taken from a longitudinal analysis performed by using data from the large Rotterdam

study conducted from 1990 to 1993 restricted to men and women older than 55. They suggested an increased intake of tea may contribute to primary prevention of ischemic heart disease.

Green tea and tea catechins have been shown to be hypolipidemic.<sup>18,29</sup> Yang and Koo treated hypocholesterolemic rats with green tea and examined the effect on HMG CoA reductase and other lipid enzymes.<sup>30</sup> They demonstrated a lowering of serum total cholesterol and elevated HDL levels. Furthermore, they demonstrated the inhibitory effect of green tea on endothelial cell-induced LDL oxidation, suggesting that green tea may delay atherogenesis and lower the risk of coronary heart disease.<sup>31</sup>

Miura et al.<sup>32,33</sup> noted that aortic cholesterol and triglyceride levels were 27% and 50% lower, respectively, over control mice after administration of green tea extract to male apoE-deficient mice. Their results suggested that chronic ingestion of tea extract prevents development of atherosclerosis without changing the plasma lipid level in apoE-deficient mice and they speculated that the mechanism is due to the potent antioxidative activity of the tea, although more specific actions may be responsible.

For heart disease protection, the potent antioxidant properties of polyphenols reduce free radical damage to cells and prevent the oxidation of LDL cholesterol, both of which would be expected to inhibit the formation of atherosclerotic plaques.<sup>29,34–38</sup>

### *Arthritis*

An antioxidant-rich polyphenolic fraction isolated from green tea has been reported to possess anti-inflammatory properties in laboratory animals.<sup>39</sup> One laboratory study reported positive benefits on collagen-induced arthritis in mice. The mice exhibited a significant reduction in the incidence of arthritis (33%) compared with mice not given green tea polyphenols (50%). Analysis showed a marked reduction in the expression of inflammatory mediators such as cyclooxygenase 2, interferon (IFN)- $\gamma$ , and tumor necrosis factor (TNF)- $\alpha$  in the arthritic joints of the mice fed green tea polyphenols. Additionally, total IgG and type II collagen-specific IgG levels were lower in the serum and arthritic joints of the treated mice.<sup>39</sup>

### *Bone density*

A study of 1256 women in the United Kingdom aged 65 to 76 (1134 tea drinkers and 122 non-tea drinkers) reported that tea drinkers had significantly greater mean bone mineral density measurements (~5%, adjusted for age and body mass index), independent of smoking status, the use of hormone replacement therapy, coffee drinking, and whether milk was added to tea.<sup>40</sup> The authors concluded that drinking tea may help protect against osteoporosis in older

women. However, an animal study has reported that tannins contained in black and green teas may decrease the absorption of calcium and iron to some extent.<sup>41</sup> In the study, green tea decreased the absorption rate of zinc while black tea reportedly increased the rate. Both teas promoted the absorption of manganese and copper.

### *Stress and theanine*

One of the reasons that green tea has been used in the Orient for centuries is its calming and curative properties due to the presence of L-theanine, an amino acid found primarily in green and black teas that produces tranquilizing effects in the brain.<sup>42,43</sup> Through the natural production of polyphenols, the tea plant converts theanine into catechins. This means that tea leaves harvested during one part of the growing season may be high in catechins (good for antioxidant benefits), while leaves harvested during another time of year may be higher in theanine. Three to four cups of green tea are expected to contain from 60 to 160 mg of theanine. Recently, L-theanine has been linked to the feelings of relaxation reported by those who drink green tea. Experimental studies have also shown that L-theanine appears to negate some of the effects of caffeine.<sup>42</sup>

L-theanine facilitates the generation of alpha waves in the brain believed to be associated with a relaxed yet alert mental state. A clinical study on L-theanine using young women subjects showed that L-theanine seemed to have the greatest impact on the production of alpha waves among those women who had been categorized as high-anxiety subjects.<sup>42</sup> Theanine is believed to lower cortisol levels during stress periods (cortisol production in the body increases during physical stress).

Research studies have found that people who produce more alpha brain waves also have less anxiety and highly creative people generate more alpha waves when faced with a problem to solve. Elite athletes tend to produce a burst of alpha waves on the left side of their brains during their best performances. One of the specific aspects of theanine activity is its ability to increase the brain's output of alpha waves. Alpha waves are one of the four basic brainwave patterns (delta, theta, alpha, and beta) that can be monitored using an electroencephalogram (EEG). Each wave pattern is associated with a particular oscillating electrical voltage in the brain, and the different brainwave patterns are associated with different mental states and states of consciousness (theta = drowsiness; alpha = relaxed/alert; beta = stress/anxiety).

Studies in rats have shown theanine to be an effective antihypertensive agent.<sup>44</sup> In these studies, it is interesting to note that theanine was able to bring elevated blood pressure back toward normal levels, but had no effect on normal blood pressure levels.<sup>45,46</sup>

Because theanine reaches its maximum levels in the blood between 30 minutes and 2 hours after ingestion, it can be

used as both a daily antistress and mental focus regimen and as needed as a supplement during stressful times.

Studies on rodents have shown that the ability to learn and remember may be enhanced with theanine supplementation.<sup>47,48</sup> This natural relaxant works to diminish stress, worry, and anxiety, and may allow the brain to focus and concentrate better.<sup>43</sup>

#### *Antiviral properties*

Tea catechins exhibit a protective effect against human immunodeficiency virus (HIV) infection, partly mediated by inhibiting virions to bind to the target cell surface.<sup>49,50</sup> Kawai et al. investigated the mechanism of the anti-HIV effect of green tea polyphenols and clearly demonstrated that EGCg (but not ECG) directly binds to the cell-surface CD4 molecules.<sup>51</sup> It remains to be seen whether these effects are seen in humans and more studies are needed.

#### *Anticariogenic effects*

Human and laboratory studies have supported the use of green tea as a preventative measure in dental caries.<sup>52,53</sup> Salivary amylase hydrolyzes food starch to low molecular weight carbohydrates (maltose) that are easily fermentable. A recent study reported that consumption of tea (black or green) inhibits the release of maltose up to 70%.<sup>54</sup> Black tea was a more potent inhibitor than green tea. Another study reported that a green tea extract was effective in reducing the gingival inflammation caused by periodontal structures such as dentures.<sup>55</sup>

An *in vitro* study reported that a green tea extract strongly inhibited *Escherichia coli*, *Streptococcus salivarius*, and *Streptococcus mutans*.<sup>56</sup> The antibacterial effects of green and black tea extracts were comparable with those of amoxicillin, cephadrine, and eugenol.

#### *Ultraviolet skin protection*

There have been several animal studies that support the use of green tea in the prevention of ultraviolet (UV)-induced skin carcinogenesis and as topical skin protection against UV radiation.<sup>57–60</sup> Similar results have been reported from *in vitro* studies on human skin.<sup>61</sup> A recent human study reported that a topical application of EGCg prior to exposure to UV radiation had preventative effects on damage to the skin.<sup>62</sup> A single UV exposure of 4 minimal erythema doses (MED) to human skin was found to increase catalase activity (109–145%) and decrease glutathione peroxidase (GPx) activity (36–54%) and total glutathione (GSH) level (13–36%) at different time points studied. Pretreatment of the skin with EGCg from green tea was found to restore the UV-induced decrease in GSH level and protection of the skin to GPx. Further studies are warranted to elucidate the preventive effects of EGCg against multiple exposures of human skin to UV light.

## CONCLUSIONS

In summary, a number of significant scientific studies have confirmed the health benefits of tea. In this review we covered noncancer health benefits of both green and black tea. In Part II, a review of anticancer properties of green tea extracts will be presented.<sup>63</sup> The green tea catechins possess various biological activities in antioxidant, anti-angiogenesis, and antiproliferative assays potentially relevant to the prevention and treatment of various forms of cancer. Although much focus has been put on the biological properties of the major tea catechin EGCg and its antitumor properties, other health benefits due to the presence of theanine and theaflavin constituents have been described. We believe that in future more studies will focus on these important constituents, further confirming a linkage between standardized extracts and a clinical target through a biological effect.

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