Green tea and its polyphenolic catechins: Medicinal uses in cancer and noncancer applications

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Abstract

Can drinking several cups of green tea a day keep the doctor away? This certainly seems so, given the popularity of this practice in East Asian culture and the increased interest in green tea in the Western world. Several epidemiological studies have shown beneficial effects of green tea in cancer, cardiovascular, and neurological diseases. The health benefits associated with green tea consumption have also been corroborated in animal studies of cancer chemoprevention, hypercholesterolemia, atherosclerosis, Parkinson’s disease, Alzheimer’s disease, and other aging-related disorders. However, the use of green tea as a cancer chemopreventive or for other health benefits has been confounded by the low oral bioavailability of its active polyphenolic catechins, particularly epigallocatechin-3-gallate (EGCG), the most active catechin. This review summarizes the purported beneficial effects of green tea and EGCG in various animal models of human diseases. Dose-related differences in the effects of EGCG in cancer versus neurodegenerative and cardiovascular diseases, as well as discrepancies between doses used in vitro studies and achievable plasma understanding of the in vivo effects of green tea catechins in humans, before the use of green tea is widely adopted as health-promoting measure.

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Introduction

Green tea has attracted significant attention recently, both in the scientific and in consumer communities for its health benefits for a variety of disorders, ranging from cancer to weight loss. This publicity has led to the increased consumption of green tea by the general and patient population, and to the inclusion of green tea extract as a featured ingredient in several nutritional supplements, including multivitamin supplements. Historically, green tea has been consumed by the Japanese and Chinese populations for centuries, and is probably the most consumed beverage besides water, in Asian society. The beneficial effects of green tea are attributed to the polyphenolic compounds present in green tea, particularly the catechins, which make up 30% of the dry weight of green tea leaves (Graham, 1992). These catechins are present in higher quantities in green tea than in black or oolong tea, because of differences in the processing of tea leaves after harvest. For green tea, fresh tea leaves from the plant Camellia sinensis are steamed and dried to inactivate the polyphenol oxidase enzyme, a process that essentially maintains the polyphenols in their monomeric forms. Black tea, on the other hand, is produced by extended fermentation of tea leaves which results in the polymeric compounds, thearubigins and theaflavins. Oolong tea is a partially fermented product and contains a mixture of the monomeric polyphenols and higher molecular weight theaflavins (Graham, 1992). All three varieties of tea contain significant amounts of caffeine (3–6%) which is unaffected by the different processing methods (Chu, 1997).

There are several polyphenolic catechins in green tea, viz. (−) epicatechin (EC), (−) epicatechin-3-gallate (ECG), (−) epigallocatechin (EGC), (−) epigallocatechin-3-gallate (EGCG), (+) catechin, and (+) gallocatechin (GC) (Fig. 1). EGCG, the most abundant catechin in green tea, accounts for 65% of the total catechin content. A cup of green tea may contain 100–200 mg of EGCG. Catechin and gallocatechin are present in trace amounts (Chu and Juneja, 1997). Most of the medicinal

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properties of green tea are associated with the ‘epi’ catechins (2R, 3R) rather than the catechins (2S, 3R) (Fig. 1).

**Health benefits of green tea**

Green tea and its constituent catechins are best known for their antioxidant properties, which has led to their evaluation in a number of diseases associated with reactive oxygen species (ROS), such as cancer, cardiovascular and neurodegenerative diseases. Several epidemiological studies as well as studies in animal models have shown that green tea can afford protection against various cancers such as those of the skin, breast, prostate and lung (Mukhtar and Ahmad, 2000; Yang et al., 2002). In addition to the cancer chemopreventive properties, green tea and EGCG have been shown to be anti-angiogenic (prevention of tumor blood vessel growth) (Cao and Cao, 1999; Pfeffer et al., 2003) and anti-mutagenic (Wang et al., 1989; Han, 1997). Green tea has also shown to be hypcholesterolemic (Yang and Youdim, 2004b) and to prevent the development of atherosclerotic plaques (Chyu et al., 2004). Among age-associated pathologies and neurodegenerative diseases, green tea has been shown to afford significant protection against Parkinson’s disease, Alzheimer’s disease, and ischemic damage (Mandel et al., 2004a). Green tea has also shown anti-diabetic effects in animal models of insulin resistance (Wu et al., 2004b) and has been shown to promote energy expenditure (Dulloo et al., 1999). Other health benefits attributed to green tea include antibacterial (Stapleton et al., 2004), anti-HIV (Nance and Shearer, 2003), anti-aging (Esposito et al., 2002) and anti-inflammatory activity (Dona et al., 2003).

**Molecular mechanisms of green tea effects**

The health benefits of green tea are mainly attributed to its antioxidant properties and the ability of its polyphenolic catechins to scavenge reactive oxygen species (Yang, 1999). These properties are due to the presence of the phenolic hydroxy groups on the B-ring in ungalloylated catechins (EC and EGC) (Fig. 1) and in the B- and D-rings of the galloylated catechins (ECG and EGCG) (Salah et al., 1995). The presence of the 3,4,5-trihydroxy B-ring has been shown to be important for antioxidant and radical scavenging activity (Nanjio et al., 1996; Valcic et al., 1999). The green tea catechins have been shown to be more effective antioxidants than Vitamins C and E (Rice-Evans et al., 1995), and their order of effectiveness as radical scavengers is EC > EG > EGC > EC > catechin. The metal-chelating properties of green tea catechins are also important contributors to their antioxidative activity (Brown et al., 1998; Hider et al., 2001; Kumamoto et al., 2001). Recent studies have shown that misregulated iron metabolism may be a central pathological feature in Parkinson’s disease and that the iron-chelating properties of EGCG are important for its protective effects in neurodegenerative diseases (Mandel et al., 2004a).

In addition to antioxidant effects, green tea catechins have effects on several cellular and molecular targets in signal transduction pathways associated with cell death and cell survival. These effects have been demonstrated in both neuronal cells and in tumor epithelial/endothelial cells (Mandel et al., 2004b; Gouni-Berthold and Sachinidis, 2004). However, it is still unclear whether these effects on molecular endpoints in signal transduction pathways are downstream events of the modulation of pro-oxidant/antioxidant balance in cells or due to the direct action of EGCG and other catechins on the various molecular targets, independent of antioxidant activities. Furthermore, most of the putative molecular mechanisms that have been proposed are based on in vitro studies at EGCG concentrations far in excess of those achievable in vivo. Whether these molecular targets are affected in vivo after green tea consumption still remains to be shown.

The understanding of the in vivo effects of green tea consumption is thus far from complete, but needs to be addressed especially since green tea consumption has gained popularity among the general population. In this context, it is interesting to observe that the beneficial effect of green tea and EGCG in neurological diseases is thought to stem from its ‘antiapoptotic/pro-survival’ effect and prevention of neuronal cell loss, whereas its effect in cancer chemoprevention and cardiovascular diseases is thought to result from its ‘proapoptotic’ effects on tumor and premalignant cells. This dichotomy is...
probably a function of the concentration of EGCG and green tea at which these effects are observed. Nonetheless, it is quite relevant to our understanding of the overall in vivo effects of green tea consumption, given the low oral bioavailability of the polyphenolic catechins after drinking green tea (Chow et al., 2001, 2003). Consequently, in vitro studies of the molecular targets of green tea and EGCG, if carefully planned to evaluate the effects at a range of concentrations, can provide an important framework for understanding their in vivo relevance.

The cancer chemopreventive properties of green tea have been attributed to its inhibition of tumor cell proliferation and molecular pathways involved in the cell cycle, angiogenesis, invasion, and growth factor-related proliferation (see Adhami et al., 2003; Lambert and Yang, 2003 for excellent reviews). EGCG treatment results in G1 growth arrest, inhibition of cyclin-dependent kinases (cdks) and induction of cdk inhibitors p21 and p27 in breast and prostate cancer cells (Gupta et al., 2004; Park and Dong, 2003). EGCG also inhibits several growth factor signaling cascades, either by direct blockade of growth factor receptors or through downstream effects (Gouni-Berthold and Sachinidis, 2004). EGCG also inhibits transcription factor-mediated gene activation such as that via NF-κB and AP-1 (Ahmad et al., 2000). Inhibition of NF-κB and AP-1-mediated gene activation is the central phenomenon that explains the convergence in the antioxidant activity of the green tea catechins and their effects on specific molecular targets. NF-κB, in response to ROS, activates transcription of many pro-inflammatory and anti-apoptotic/survival genes (Schoonbroodt and Piette, 2000). The ROS-scavenging activity of green tea catechins (Levites et al., 2002b) inhibits NF-κB activation, leading to inhibition of expression of these pro-inflammatory and survival genes. In addition, EGCG has been shown to directly inhibit proteasome activity (Nam et al., 2001), leading to accumulation of the NF-κB inhibitory protein, Iκ-B, and other pro-apoptotic proteins such as Bax. Inhibition of NF-κB-mediated gene activation is also the likely mechanism of inhibition of inducible nitric oxide synthase observed with green tea and EGCG, which mediates its anti-inflammatory actions (Singh et al., 2002). Green tea also inhibits angiogenesis and tumor invasion by inhibiting metalloproteinases and the vascular endothelial growth factor receptor expression and signaling in tumor and endothelial cells, respectively (Jung et al., 2001; Masuda et al., 2002; Kojima-Yuasa et al., 2003; Waleh et al., 2005).

In neuronal cells, however, green tea catechins serve a neuroprotective pro-survival function. Moreover, these effects have been observed at doses far lower than those at which antitumor activities have been demonstrated (Mandel et al., 2004b). Although many of the molecular effects of green tea in neuronal cultures can be attributed to its antioxidant and metal-chelating activity at low doses, evidence now suggests that tea catechins also affect discrete cell signalling pathways in neuronal cells, leading to a neuroprotective effect (Weinreb et al., 2003; Mandel et al., 2003). EGCG, at doses of 1–10 μM, was shown to protect against amyloid-β- and 6-hydroxydopamine-induced neuronal cell death by activation of protein kinase C (PKC) (Levites et al., 2002a; 2003). PKC plays a central role in neuronal cell survival and loss of PKC activity is a frequent consequence of neuronal insults such as amyloid-β accumulation and other neurotoxins (Liu and Heckman, 1998; Maher, 2001). Low doses of EGCG were recently shown to decrease expression of the proapoptotic genes bax, bad, caspases, and p21 in neuronal cells (Levites et al., 2002b; Weinreb et al., 2003), suggesting a pro-survival neuroprotective effect of EGCG in the brain. EGCG also affects the processing of amyloid precursor protein (APP) via multiple mechanisms. EGCG has been shown to promote APP processing via the non-amyloidogenic α-secretase pathway (Levites et al., 2003) and also appears to directly inhibit the β-secretase pathway that leads to the formation of β-amyloid fibrils (Jeon et al., 2003).

It is clear that the cellular effects of EGCG and green tea are dose- and cell-type dependent and that they involve more than just its antioxidant and radical-scavenging activity. Which of these effects are manifested in vivo will also depend on the dose (intake) and pharmacokinetics of green tea. Since green tea is gaining popularity as a health-promoting natural product, it is important to study the relevant mechanisms of action of green tea in a dose- and cell-type dependent fashion, and to correlate studies that have been carried out in tumor cells versus neuronal cells, to put into perspective the overall in vivo effects of green tea consumption. Such studies remain to be done. Nevertheless, the fact that green tea has been used for centuries by Asian cultures without toxicity, and the myriad of health problems that green tea is purported to abate, suggests that the polyphenolic catechins, particularly EGCG, in this natural product (nutraceutical), may provide good lead compounds for the discovery of novel pharmaceutical agents. Ideally, such agents should mimic the protective effects of green tea, but not suffer from the liabilities associated with using undefined natural product mixtures, or require major lifestyle changes (such as drinking several cups a day) to obtain the health benefits that green tea confers. The discussion below presents an overview of the potential applications of green tea and its catechins in a variety of disorders and highlights the potential applications of green tea-based therapeutics.

Green tea in aging and neurodegenerative diseases

Aging

According to the free radical theory of aging (Harman, 1994), increased free radical generation and oxidative stress are the basis for phenotypic changes that lead to age-associated functional deterioration and neurodegeneration. Several age-associated diseases such as cancer, Parkinson’s disease, Alzheimer’s disease, cardiovascular diseases, and diabetes have their etiologies linked to changes in oxidant/anti-oxidant balances and free radical damage (Polidori, 2003; Junqueira et al., 2004). However, Kitani et al. (2004) report that green tea as the sole source of liquid did not significantly increase life span in mice, compared to controls. However, green tea did protect against ethanoll-induced oxidative stress in aged mice, and prevented serum lipids and protein from oxidative damage, produced by ethanol and enhanced by aging.
Interestingly, using an aged mouse model of accelerated senescence (SAMP10 mice), Unno et al. (2004) demonstrated that green tea catechins, when administered in drinking water, had a protective effect on cognitive dysfunction and suppressed cerebral atrophy in these animals. Furthermore, green tea also decreased the levels of 8-oxo-deoxyguanosine (8-oxodG), a marker of oxidative DNA damage, in the kidney, liver and cerebrum, suggesting that green tea polyphenols may have a beneficial effect on the damage from the aging process.

Parkinson’s disease

Oxidative stress is believed to be a major contributor to the pathogenesis of Parkinson’s disease, especially the death of dopaminergic neurons (Olanow and Tatton, 1999). Recently, misregulated iron metabolism in the brain has been shown to be involved in the generation of the pathological Lewy bodies in Parkinson’s disease through iron-induced aggregation of alpha-synuclein (Kaur and Andersen, 2004). In well-established Parkinson’s disease through iron-induced aggregation of alpha-synuclein (Kaur and Andersen, 2004). In well-established Parkinson’s disease, neurotoxins 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) induce dopaminergic cell death and accumulation of Lewy bodies, mediated through several mechanisms involving oxidative stress. Various studies have shown that green tea and EGCG significantly prevent these pathologies in animal models (Levites et al., 2001). EGCG, administered orally in doses as low as 25 mg/kg, prevented loss of dopaminergic neurons in the substantia nigra and preserved striatal levels of dopamine (Choi et al., 2002). Recently, Mandel et al. (2004a) also showed that EGCG prevented the accumulation of iron and alpha-synuclein in MPTP-treated mice. These effects have been attributed to the antioxidant activity and iron-chelating properties of EGCG, respectively. Although several in vitro studies have also implicated other pathways of neuroprotection, such as the enhancement of PKC phosphorylation and inhibition of pro-apoptotic genes (discussed above), particularly at low EGCG concentrations, these effects have yet to be established in vivo. Nevertheless, Choi et al. (2002) demonstrated decreased expression of neuronal nitric oxide synthase (nNOS) in their MPTP-induced Parkinson’s mouse model. Epidemiological studies on the prevalence of Parkinson’s disease and green tea consumption do show a 5- to 10-fold lower incidences of the disease in Asian populations (Zhang and Roman, 1993; Pan et al., 2003), although several other studies show a protective effect of iron chelators and antioxidants in general (Youdim et al., 2000; Sanz et al., 2004; Zheng et al., 2005).

Alzheimer’s disease

Although there is no epidemiological evidence in human studies of the benefit of green tea for Alzheimer’s disease, several studies in animal and cell culture models suggest that EGCG from green tea may affect several potential targets associated with Alzheimer’s disease progression. Choi et al. (2001) showed that EGCG protects against beta-amyloid-induced neurotoxicity in cultured hippocampal neurons, an effect attributed to its antioxidant properties. In addition, Levites et al. (2003) recently showed that EGCG regulates the processing of APP, through PKC activation, to the non-amyloidogenic soluble APP (sAPP), thus preventing the formation of the neurotoxic beta-amyloid. EGCG and other green tea catechins have also been shown to inhibit the beta-secretase enzyme (BACE1) (Jeon et al., 2003) that is responsible for processing sAPP to beta-amyloid, thus having a potentially synergistic inhibitory effect on the production of beta-amyloid. This effect on the processing of sAPP was also demonstrated in vivo in mice given 2 mg/kg/day of EGCG for 7–14 days. Thus, the inhibitory effect of green tea catechins on Alzheimer’s disease targets and the neuroprotective effect of their antioxidant activity strongly suggest that these catechins have potential application in the treatment of Alzheimer’s disease.

Stroke

EGCG has been shown to afford protection against neuronal damage after ischemia in gerbils, when administered systemically at 50 mg/kg immediately after excitotoxic ischemic insult (Lee et al., 2004). At this dose, EGCG was also found to exhibit a significant antioxidant effect in rats and protected against neurological deficit and infarction due to the focal ischemia, when administered 24 h after a transient cerebral occlusion (Choi et al., 2004). When administered in drinking water days before ischemic damage in rats, green tea extract also has an antioxidant effect and protects against neurologic deficits (Suzuki et al., 2004) suggesting that drinking green tea can have neuroprotective benefits, and that EGCG may also have application as a neuroprotective agent against acute ischemic damage.

Green tea and cardiovascular diseases

Green tea consumption has been associated with a lower incidence of coronary artery disease in Japanese populations (Sano et al., 2004). The protective effect of green tea in cardiovascular diseases is also thought to stem from its antioxidant activity (see Higdon and Frei, 2003, for a comprehensive review). Indeed, Miura et al. (2000) showed that oral intake of green tea extract by human volunteers increased resistance of plasma LDL to oxidation in vivo, an effect that may lower the risk of artherogenesis. In the apolipoprotein E-deficient mouse model of atherosclerosis, green tea extract administered in drinking water, prevented the development of atherosclerosis without affecting plasma lipid or cholesterol levels (Miura et al., 2001). Similarly, EGCG at a dose of only 10 mg/kg given intraperitoneally significantly inhibited the developing atherosclerotic plaques in Apo E-deficient mice, but had no effect on established lesions (Chyu et al., 2004). Green tea extract also attenuated blood pressure increases in spontaneously hypertensive rats, an effect attributed to its antioxidant properties (Negishi et al., 2004). While these studies suggest that drinking green tea may protect against cardiovascular diseases, drug interactions between green tea and cardiovascular therapy are possible, particularly in the
Western world, where the use of cardiovascular drugs is widespread (Izzo et al., 2005). These factors thus need to be considered before drinking green tea for health benefits is widely promoted in Western society.

Green tea, obesity and weight loss

Several studies have suggested that oral consumption of green tea may protect against obesity-related disorders such as atherosclerosis, diabetes, and hypertension. Interestingly, Kao et al. (2000) showed that purified EGCG (50–100 mg/kg), but not other green tea catechins, significantly reduced or prevented an increase in body weight in lean and obese Zucker rats, an effect that appeared to be reversible and associated with a reduction in food intake. Given the in vivo effects of purified EGCG on other related parameters, such as inhibition of lipid oxidation and modulation of glucose levels (Tsuneki et al., 2004), EGCG may be a useful candidate for treating obesity. These potential uses of EGCG remain to be explored.

Green tea and diabetes

Insulin resistance and glucose intolerance, features of Type 2 diabetes, are also considered risk factors for cardiovascular disease and for metabolic syndrome X (a combination of disorders afflicting Western society) (Reaven, 1988). In a small study in human volunteers, Tsuneki et al. (2004) found that drinking green tea substantially increased oral glucose tolerance but did not affect basal blood glucose levels. Long-term administration of green tea extract to normal rats increased insulin sensitivity (Wu et al., 2004a). When administered to fructose-fed rats, green tea extract was also found to prevent development of insulin resistance, hyperglycemia and other metabolic defects (Wu et al., 2004b). It has been demonstrated in vitro that these effects were due to increased insulin sensitivity and glucose uptake of adipocytes and that EGCG was the most active catechin component that showed these effects (Anderson and Polansky, 2002; Wu et al., 2004a). Thus, green tea may also be useful in controlling metabolic syndrome X.

Green tea and cancer

Green tea is perhaps best known and most studied for its effects on cancer chemoprevention. However, the results of epidemiological studies in humans have been inconsistent; some studies have shown reduced cancer incidence and recurrence associated with green tea consumption, whereas others have failed to show an effect. Several recent reviews compiling results of such studies are available (Kim and Masuda, 1997; Yang et al., 2002). On the other hand, studies in animal models of carcinogenesis are far more convincing and have clearly demonstrated the preventive effects of green tea and EGCG against tumorigenesis in the breast, prostate, lung and skin. This convincing evidence perhaps led to the selection of green tea extract by the National Cancer Institute (NCI) for further development as a cancer chemopreventive (Steele et al., 1999). Decaffeinated green tea extract, available as POLYPHENON E, is currently in Phase II clinical trials. Phase I trials with single- and multiple-dose administration in healthy subjects and in patients with solid tumors have shown that the oral bioavailability of tea catechins is extremely low (<1%) and that the catechins undergo extensive metabolism (Chow et al., 2001, 2003; Lee et al., 2002; Pisters et al., 2001; Laurie et al., 2005). This poor pharmacokinetics profile requires one to drink several cups of green tea a day or ingest large doses of POLYPHENON E to obtain cancer preventive benefits.

It is still not clear if the cancer preventive activity of green tea is due to its antioxidant activity. Although modest and transient increases in plasma antioxidant capacity with green tea consumption have been reported (Higdon and Frei, 2003), its contribution to the inhibition of carcinogenesis is yet to be established. However, Hakim et al. (2003) have recently shown that drinking as many as 4 cups of green tea a day decreases levels of 8-OHdG, a marker of oxidative DNA damage, in former smokers. As with any human trials with cancer preventive agents, the effect of these changes on the incidence or occurrence of cancer is difficult to establish (Moyers and Kumar, 2004).

Studies in animal models have demonstrated that green tea and EGCG can inhibit carcinogenesis at all stages, viz. initiation, promotion and progression (Chung et al., 2003). This multifaceted inhibition of the tumorigenic process is attributed to a combination of antioxidative, antiproliferative and pro-apoptotic effects (Gouni-Berthold and Sachindis, 2004; also see above). Green tea and EGCG have also been shown to inhibit the process of angiogenesis, tumor metastasis and invasion in animal models (Fassina et al., 2004; Jung and Ellis, 2001; Garbisa et al., 2001). It is likely that species differences in the pharmacokinetics of green tea and EGCG in humans and rodents may account for the more definitive evidence of the cancer chemopreventive effect of green tea in animal models (Kim et al., 2000). One other confounding factor in our understanding of the role of green tea in cancer chemoprevention is that most in vitro studies of mechanism of action use doses of EGCG and green tea far in excess of established human plasma levels. Thus, the relevance of the various mechanisms of antiproliferative, anti-angiogenic, and anti-inflammatory activities of green tea and catechins, to the prevention of carcinogenesis in humans, represents a monumental challenge, yet to be addressed (Yang et al., 1999).

Green tea and microbial diseases

Green tea has been known to prevent dental caries for decades. However, recently, EGCG has received significant attention for its effects on inhibition of HIV infection and multidrug-resistant Staphylococcus aureus infections (Nance and Shearer, 2003; Stapleton et al., 2004). EGCG has been shown to inhibit HIV-1 replication by inhibiting HIV reverse transcriptase and by interfering with the binding of the viral envelope. Recently, Kawai et al. (2003) showed that EGCG prevents the attachment of the HIV-1 virion, gp120, to the CD4 molecules on T-helper cells, thus preventing the initial step in the HIV-1 infection process. However, in vitro studies with pure...
EGCG need to be interpreted with caution, since the stability of EGCG in cell culture media is questionable (Hong et al., 2002; Naasani et al., 2003). EGCG’s polyphenolic nature and its high affinity for protein may also confound the results of in vitro experiments that use pure EGCG. Interestingly, EGCG and another galloyl-containing catechins were also identified in a high-throughput screening assay as inhibitors of scrapie-associated prion protein formation (Kocisko et al., 2003).

Conclusions

While it is clear that drinking green tea may improve general well-being in humans, this practice may not be as easily adopted in Western society. Although decaffeinated green tea extracts have been marketed as nutritional supplements (POLYPHENON E, TEAVIGOTM), large doses need to be used because of the poor pharmacokinetic profiles of the active polyphenolic catechins. In addition, using natural product mixtures as nutraceutical supplements is always associated with risks of drug interactions with any of the multiple components of such a mixture, particularly if used with conventional therapy, as is most often the case. On the other hand, considerable information is available on the interaction of EGCG with various molecular targets in cancer, cardiovascular disease and neurological diseases. As with other natural products, EGCG and other green tea catechins can perhaps be useful lead compounds for new drug discovery against the various putative molecular targets. Rational design of analogs of such catechins would also be valuable for structure-activity relationship studies to determine the contribution of the various phenolic groups to the antioxidant activity and the overall therapeutic effects of green tea (Zaveri, 2001).

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