

Green Tea Polyphenols and Cancer: Biologic Mechanisms and Practical Implications

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Polyphenolic compounds in fruits and vegetables have been associated with lower risk of some diseases, including cancer. Recent research has shown that the polyphenolic antioxidants in green tea possess cancer chemopreventive effects. This review discusses the cancer chemopreventive effects associated with green tea and the molecular mechanisms that underlie the broad anticarcinogenic effect of polyphenols in green tea.

Introduction

Plants, including herbs and their derivatives, have been used to combat a variety of ailments.¹⁻⁵ The polyphenols present in these botanicals (fruits, vegetables, herbs, etc.) appear to be partially responsible for many of the protective effects of plants against a variety of diseases, including cancer.¹⁻⁶ More than 6 million people die of cancer each year, and it is among the leading causes of death in both men and women worldwide.⁷ Several human cohort and case-control studies, as well as a variety of animal studies, have suggested that polyphenols possess significant chemopreventive properties,¹⁻⁹ due perhaps to their antioxidant activity.

Polyphenols and Cancer

Several animal studies have demonstrated an anticarcinogenic effect of polyphenols.^{3,8-10} Some of the polyphenols studied for their anticarcinogenic potential are flavones, flavonols, isoflavones, and catechins. Tannins, present in many plant foods, have also been shown to possess anticarcinogenic and antimutagenic potentials.³ The lower incidence of certain types of cancer in Mediterranean countries is considered to be associated with that region's high consumption of olive oil,

which contains polyphenolic compounds such as hydroxytyrosol and oleuropein.¹¹ Curcumin, a yellow coloring agent present in the spice turmeric, and ellagic acid, a polyphenol abundant in fruits (especially berries), nuts, and vegetables, have been shown to afford protection against chemical carcinogenesis in animals.¹² Recent studies have shown that resveratrol (3,5,4'-trihydroxystilbene), a polyphenolic antioxidant found in grapes, red wine, berries, and peanuts, exhibits chemopreventive effects in mice.⁷ Recently, tea derived from the *Camellia sinensis* plant, which contains many polyphenolic compounds, has also been shown to protect against a variety of ailments, including cancer.^{8,9,13}

History, Consumption, and Chemistry of Tea

The tea plant *Camellia sinensis* is believed to have been originally discovered and grown in Southeast Asia. Tea consumption can be traced back to 2737 B.C., when, as believed by the Chinese, the emperor of China, Shen Nung, discovered and used tea for the first time.¹⁴ Because of its characteristic flavor and the health-promoting effects associated with it, tea consumption rapidly spread worldwide and the tea plant is currently cultivated in approximately 30 countries. Although consumption levels vary widely around the world, it is believed that tea consumption is second only to water, with a per capita human consumption of approximately 120 mL/day.^{8,9} Many types of tea plant preparations are made from *C. sinensis*, and different forms of processing are available today. The two major types of tea consumed are black tea (78%), which is predominant in Western countries and some Asian countries, and green tea (20%), which is predominant in China, Japan, India, and a few countries in North Africa and the Middle East.^{8,9}

The chemical composition of green tea, with regard to its major components, is similar to that of the fresh leaves of the plant. It contains many polyphenolic compounds, which account for up to 30% of the dry weight of green tea leaves. Most of the polyphenols in green tea are flavanols, commonly known as catechins.^{8,9} The primary catechins in green tea are epicatechin, epicatechin-3-gal-

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late (ECG), epigallocatechin (EGC), and epigallocatechin-3-gallate (EGCG). The chemical structures of these compounds are illustrated in Figure 1. In addition, caffeine, theobromine, theophylline, and phenolic acids, such as gallic acid, are also present as minor constituents of green tea.⁸

Black tea also contains several polyphenols, such as bisflavanols, theaflavins, and thearubigens.⁸ Many of these are generated as a result of oxidation of the flavanols in tea leaves by the enzyme phenol oxidase. Theaflavins (1–2% of dry weight) contain benzotropolone rings with dihydroxy or trihydroxy substitution systems. About 10–20% of the dry weight of black tea is attributed to thearubigens, which are even more extensively oxidized and polymerized.

Green Tea and Cancer Chemoprevention

The anticarcinogenic and antimutagenic properties of green tea were first elucidated a decade ago.^{15,16} Since then, several laboratory and epidemiologic studies have been conducted.^{8,9,17} It has been demonstrated in mice that oral consumption or topical application of green tea and/or its polyphenolic constituents affords protection against carcinogenesis induced by chemicals or ultraviolet radiation.¹⁸ Polyphenols isolated from green tea or water extract of green tea have been shown in other animal models to afford prevention against chemically induced carcinogenesis in lung, forestomach, esophagus, duodenum, pancreas, liver, breast, and colon.^{8,9,19} On the basis of some recent studies, it is now believed that much of the cancer chemopreventive effects of green tea are mediated by EGCG, which is the major polyphenolic constituent of green tea.^{8,9} One cup of brewed green tea contains up to 200 mg EGCG. A recent bioavailability study²⁰ showed that frequent consumption of green tea results in high levels

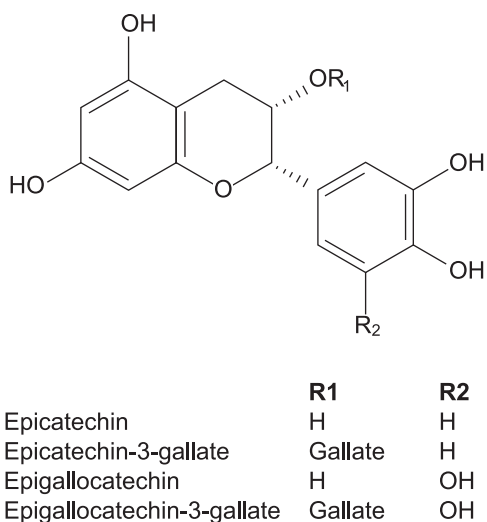


Figure 1. Major polyphenols in green tea.

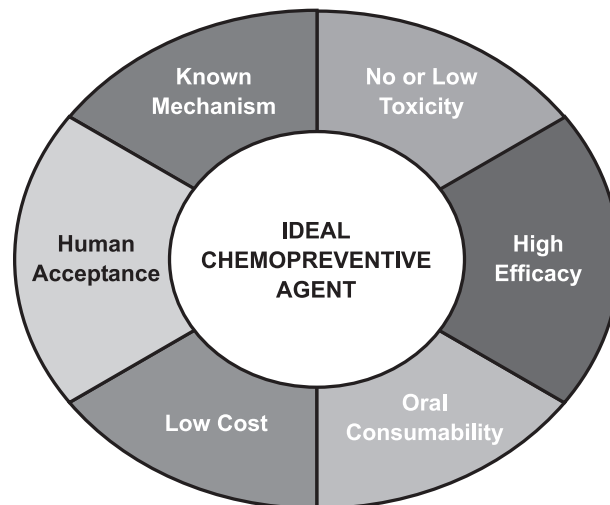


Figure 2. Qualities of an ideal chemopreventive agent.

of EGCG in various body organs, indicating that green tea consumption might protect against cancers of multiple body sites.

The anticancer and anti-inflammatory properties of green tea have interested the food, beverage, and cosmetic industries. Many consumer products, including beverages, foods, health care products, and cosmetics, are now supplemented with extracts of green tea, indicating its human acceptability. Green tea is also believed to possess most, if not all, the qualities of an ideal chemopreventive agent (Figure 2).

In addition to imparting preventive and therapeutic effects, green tea has also been shown to modulate and increase the efficacy of cancer chemotherapeutic drugs. Sadzuka et al.²¹ demonstrated recently that the oral administration of green tea resulted in enhanced tumor inhibitory effects of doxorubicin on Ehrlich ascites carcinomas implanted in CDF₁ and BDF₁ mice. Of interest is that this study showed that green tea treatment resulted in an increase in the level of doxorubicin in tumor but not in normal tissue. If these data could be verified in humans, it may have relevance to cancer chemotherapy.

Mechanisms Associated with the Biologic Effects of Green Tea

Despite recent research findings, the understanding of the mechanisms involved in the biologic effects of green tea is far from complete but nonetheless important, because understanding these mechanisms may be helpful in designing better strategies for preventing and treating cancer. The initial mechanistic studies focused on the following areas: (1) prevention of mutagenicity and genotoxicity, (2) inhibition of biochemical markers of tumor initiation and promotion, (3) effects on detoxification enzymes, (4) trapping of activated metabolites of carcino-

gens, and (5) antioxidant and free-radical scavenging activity. Recent research efforts are described below.

Activation of the Mitogen-activated Protein Kinase Pathway by Green Tea

Results of initial mechanistic studies attributed the protective effects of green tea polyphenols to the competitive inhibition of enzymes such as cytochrome P450, which is involved in the bioactivation of carcinogens.²² These and other *in vivo* studies demonstrated the involvement of phase II detoxifying enzymes in the biologic response of green tea. The 5' flanking regions of phase II genes contain several *cis*-acting regulatory elements, including the antioxidant-responsive element (ARE), which is thought to mediate the induction of phase II enzymes by many drugs. Yu et al.²² studied the involvement of the mitogen-activated protein kinase (MAPK) pathway, which consists of a protein kinase cascade linking growth signals with transcription in nucleus, as a mechanism of biologic response of green tea polyphenols and demonstrated that the activation of the MAPK pathway by green tea polyphenols might be responsible for the regulation of ARE-mediated phase II enzyme gene expression. This study demonstrated that treatment with green tea polyphenols of human hepatoma HepG2 cells transfected with a plasmid construct containing ARE and a minimal glutathione S-transferase Ya promoter linked to the CAT reporter gene results in induction of chloramphenicol acetyltransferase (CAT) activity. These results suggest that green tea polyphenols stimulate the transcription of phase II detoxifying enzymes via ARE. This study also demonstrated that the treatment of HepG2 cells with green tea polyphenols results in the activation of MAPK as well as extracellular signal-regulated kinase 2 (ERK2) and c-Jun N-terminal kinase 1 (JNK1), which are two major classes of the MAPK family. Furthermore, treatment also increased mRNA levels of the immediate-early genes *c-jun* and *c-fos*.

Inhibition of Urokinase Activity by EGCG

In a recent study, Jankun et al.²³ suggested that the anticancer activity of EGCG might be due to the inhibition of the enzyme urokinase, which is one of the most frequently expressed enzymes in human cancers. Employing sophisticated computer-based molecular modeling techniques, the authors demonstrated that EGCG binds to urokinase and thereby blocks His 57 and Ser 195 of the urokinase catalytic triad and extends toward Arg 35 from a positively charged loop of urokinase. These calculations were verified by quantifying the inhibition of urokinase enzyme activity by spectrophotometric amidolytic assay. The validity of these results, however, was later challenged by Yang.²⁴

Induction of Apoptosis and Cell Cycle Arrest by Green Tea

Apoptosis is a physiologic process involved in maintaining homeostasis in the living system. It has become a challenging issue in biomedical research because the life span of both normal and cancer cells within a living system is significantly affected by the rate of apoptosis.²⁵ Also known as programmed cell death, apoptosis is a discrete form of cell death different from necrosis and is regarded as an ideal way of cell elimination. Chemopreventive agents capable of modulating apoptosis and thereby affecting the steady-state cell population may therefore be useful in the management and therapy of cancer. Studies have shown that several cancer chemopreventive agents may induce apoptosis, whereas several tumor-promoting agents inhibit apoptosis.²⁶⁻²⁸ It is reasonable to assume that chemopreventive agents, which possess proven efficacy in animal tumor bioassay systems and/or human epidemiology and can cause apoptosis of cancer cells, may have a wider use in the management and control of cancer. Only a limited number of chemopreventive agents are known to cause apoptosis.^{29,30} Ahmad et al.³¹ showed recently that EGCG induces apoptosis and cell cycle arrest in human epidermoid carcinoma cells A431. Of interest is that the apoptotic response of EGCG was specific only to the cancer cells, as the phenomenon of apoptosis was also observed in human carcinoma keratinocytes HaCaT, human prostate carcinoma cells DU145, and mouse lymphoma cells LY-R, but not in normal human epidermal keratinocytes.

The differential effect of EGCG was later verified by another study in which Chen et al.³² compared the effect of EGCG on the growth of SV40 virally transformed WI38 human fibroblasts (WI38VA) with that of normal WI38 cells. Treatment with EGCG inhibited the growth of the transformed WI38VA cells but had little or no inhibitory effect on the growth of normal WI38 cells. A similar differential growth inhibitory effect was also observed in human colorectal cancer cells (Caco-2), breast cancer cells (Hs578T), and their respective normal counterparts. This study further demonstrated that EGCG induces apoptosis in WI38VA cells but not in WI38 cells. The mechanism of this differential apoptotic response was also assessed, and EGCG was found to enhance the serum-induced expression of *c-fos* and *c-myc* genes in the transformed WI38VA cells but not in normal WI38 cells.

In another study, Fujiki et al.³³ demonstrated that EGCG and other tea polyphenols inhibit the growth of human lung cancer cells PC-9 and cause a G2/M phase arrest of the cell cycle. In this study, ³H EGCG administered in mouse stomach resulted in small amounts of ³H activity in various organs, such as skin, stomach, duodenum, colon, liver, lung, and pancreas. This study suggested that the involvement of the tumor necrosis factor- α (TNF- α) pathway was a mechanism of EGCG action.

Inhibition of Cell Proliferation and Tumor Progression Through Epidermal Growth Factor Receptor Binding by EGCG

The activation of epidermal growth factor receptor (EGFR)—tyrosine kinase by its ligand is believed to initiate multiple cellular responses associated with mitogenesis and cell proliferation, and the overexpression of EGFR may produce a neoplastic phenotype. Liang et al.³⁴ recently studied the effect of EGCG on EGFR and other growth factor receptors, such as platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR). EGCG significantly inhibited DNA synthesis and protein tyrosine kinase activities of EGFR, PDGFR, and FGFR but not of pp60^{v-src}, protein kinase C (PKC), and protein kinase A (PKA) in A431 cells. EGCG also inhibited the autophosphorylation of EGFR by its ligand EGF and blocked the binding of EGF to its receptor. These results suggest that EGCG might inhibit tumor development by blocking growth factor-associated signal transduction pathways.

EGCG-mediated Inhibition of Nitric Oxide Synthase by Down-regulation of Lipopolysaccharide-mediated Activation of Transcription Factor Nuclear Factor- κ B

Nitric oxide (NO) is a short-lived bioactive molecule that is thought to play an important role in the physiology and pathophysiology of a variety of systems. Because NO is known to play key roles in inflammation and carcinogenesis, Lin and Lin³⁵ investigated the effects of green tea polyphenols on inducible NO synthase in thioglycollate-elicited and lipopolysaccharide (LPS)-activated peritoneal macrophages. Gallic acid, EGC, and EGCG significantly inhibited the protein expression of inducible NO synthase as well as the production of NO. This study also demonstrated that EGCG blocks the activation of transcription factor nuclear factor- κ B (NF κ B), which is associated with the induction of inducible NO synthase. These data suggest that EGCG blocks the induction of NO synthase by inhibiting the binding of transcription factor NF κ B to the inducible NO synthase promoter, thereby inhibiting the induction of NO synthase transcription. These results were verified by Chan et al.,³⁶ who demonstrated that EGCG inhibits lipopolysaccharide-activated and interferon γ -activated inducible NO synthase mRNA expression in cell culture systems. EGCG also inhibited the enzyme activities of inducible NO synthase and neuronal NO synthase.

Because peroxynitrite is a highly toxic oxidizing and nitrating species that is produced in vivo by the reaction between superoxide radical and NO, Pannala et al.³⁷ studied the ability of green tea polyphenols (catechin, epicatechin, ECG, EGC, and EGCG) to inhibit peroxynitrite-mediated nitration of tyrosine and to limit surface charge

alteration of low-density lipoprotein (LDL). All the compounds tested were found to be potent peroxynitrite scavengers, because they effectively prevented the nitration of tyrosine. These polyphenols were also found to protect against peroxynitrite-mediated modification of LDL.

Inhibition of Tumor Promoter-mediated Activator Protein-1 Activation by EGCG

Studies have suggested that the activation of activator protein-1 (AP-1) by phorbol ester-type tumor promoters plays an important role in tumor promotion. Because of the key role of AP-1 in tumor promoter-induced transformation of mouse epidermal cells JB6, and the antitransformation effect of tea polyphenols, Dong et al.³⁸ hypothesized that the anti-tumor promotion activity of EGCG or theaflavins is mediated by the inhibition of AP-1 activity. Using JB6 cells (a system that has been used extensively as an in vitro model for tumor promotion studies), the researchers found that EGCG and theaflavins inhibited EGF- or TPA-induced cell transformation in a dose-dependent manner. EGCG and theaflavins were also found to inhibit AP-1-dependent transcriptional activity and DNA-binding activity. Furthermore, this study demonstrated that the inhibition of AP-1 activation occurs via the inhibition of a pathway dependent on c-Jun NH₂-terminal kinase, but not on an ERK1- or ERK2-dependent pathway. Currently, the down-regulation of AP-1 activity is being increasingly appreciated as a general therapeutic strategy against cancer.³⁹

Inhibition of Protein Tyrosine Kinase Activity, *c-jun* mRNA Expression, and JNK1 Activation by EGC

Lu et al.⁴⁰ recently investigated the mechanisms of the antiproliferative effect of green tea polyphenols in vascular smooth muscle cells. All of the polyphenols studied were shown to inhibit in a dose-dependent fashion the proliferative response stimulated by serum in rabbit cultured vascular smooth muscle cells. Catechin and epicatechin were less effective in inhibiting the serum-stimulated smooth muscle cell proliferation, whereas EGC inhibited in a dose-dependent manner the proliferative responses in different cells, including rat aortic smooth muscle cells (A7r5 cells), rabbit cultured aortic smooth muscle cells, human coronary artery smooth muscle cells, and human CEM lymphocytes. The membranous protein tyrosine kinase activity stimulated by serum in A7r5 cells was found to be reduced by EGC. EGC also reduced the levels of tyrosine phosphorylated proteins with different molecular weights, thereby indicating that EGC might inhibit protein tyrosine kinase activity or stimulate protein phosphatase activity. It was also demonstrated that EGC inhibited *c-jun* mRNA levels, protein expression of phos-

phorylated JNK1 (but not phosphorylated ERK1 and ERK2), and JNK1-kinase activity. These data suggest that the antiproliferative effect of EGC may be mediated through inhibition of protein tyrosine kinase activity, reducing *c-jun* mRNA expression and inhibiting JNK1 activation.

In another study, by Kennedy et al.,⁴¹ EGC and EGCG inhibited the viability of Ehrlich ascites tumor cells. Tyrosine phosphorylation was evaluated as a mechanism of decrease in cell viability. EGC but not EGCG was found to cause a stimulation of protein tyrosine kinase activity. EGC also resulted in the tyrosine phosphorylations of 42 kDa and 45 kDa proteins and in ornithine decarboxylase activity, which is a key enzyme in polyamine biosynthesis in cells.

Conclusions

Several laboratory and epidemiologic studies have identified more than 30 classes of agents that show promise for cancer chemoprevention. Among these agents, dietary polyphenols have received much attention recently. Polyphenols in food and beverages, such as green tea, have been shown to have anticarcinogenic properties. Although many epidemiologic studies have suggested an inverse association between green tea consumption and cancer risk, a few have indicated a positive association as well. This is not surprising, because tea is consumed at varying temperatures and in various ways. The limitation of the human epidemiologic studies conducted so far is that they are mainly case-control studies and rely heavily on questionnaires, interviews, and subject responses. Comprehensive, in-depth cohort studies are needed to thoroughly evaluate the association between green tea consumption and cancer risk. Because tea is one of the most popular beverages in the world and may possess many chemopreventive qualities, it would be appropriate to conduct clinical trials with humans to evaluate the efficacy of green tea polyphenols for cancer prevention and therapy. Indeed, some phase I clinical trials to evaluate the possible efficacy of green tea in patients with advanced solid tumors are currently under way.

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1. Pezzuto JM. Plant-derived anticancer agents. *Biochem Pharmacol* 1997;53:121–33
2. Dragsted LO, Strube M, Larsen JC. Cancer-protective factors in fruits and vegetables: biochemical and biological background. *Pharmacol Toxicol* 1993;72:116–35
3. Chung KT, Wong TY, Wei CI, et al. Tannins and

- human health: a review. *Crit Rev Food Sci Nutr* 1998;38:421–64
4. Ren S, Lien EJ. Natural products and their derivatives as cancer chemopreventive agents. *Prog Drug Res* 1997;48:147–71
5. Challa A, Ahmad N, Mukhtar H. Cancer prevention through sensible nutrition. *Int J Oncol* 1997;11:1387–92
6. Kelloff GJ, Hawk ET, Crowell JA, et al. Strategies for identification and clinical evaluation of promising chemopreventive agents. *Oncology* 1996;10:1471–88
7. Jang M, Cai L, Udeani GO, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* 1997;275:218–20
8. Ahmad N, Katiyar SK, Mukhtar H. Cancer chemoprevention by tea polyphenols. In: Ioannides C, ed. *Nutrition and chemical toxicity*. West Sussex, England: John Wiley & Sons, 1998;301–43
9. Katiyar SK, Mukhtar H. Tea in chemoprevention of cancer: epidemiologic and experimental studies. *Int J Oncol* 1996;8:221–38
10. Yang CS, Lee MJ, Chen L, et al. Polyphenols as inhibitors of carcinogenesis. *Environ Health Perspect* 1997;105:971–6
11. Visioli F, Bellomo G, Galli C. Free radical-scavenging properties of olive oil polyphenols. *Biochem Biophys Res Commun* 1998;247:60–4
12. Stoner GD, Mukhtar H. Polyphenols as cancer chemopreventive agents. *J Cell Biochem* 1995;22:169–80
13. Weisburger JH. Tea antioxidants and health. In: Cadenas E, Packer L, eds. *Handbook of antioxidants*. New York: Marcel Dekker, Inc., 1996;469–86
14. Harbowy ME, Balentine DA. Tea chemistry. *Crit Rev Plant Sci* 1997;16:415–80
15. Khan WA, Wang ZY, Athar M, et al. Inhibition of the skin tumorigenicity of (+/-)-7 beta,8 alpha-dihydroxy-9 alpha,10 alpha-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene by tannic acid, green tea polyphenols and quercetin in Sencar mice. *Cancer Lett* 1988;42:7–12
16. Wang ZY, Khan WA, Bickers DR, et al. Protection against polycyclic aromatic hydrocarbon-induced skin tumor initiation in mice by green tea polyphenols. *Carcinogenesis* 1989;10:411–5
17. Kohlmeier L, Weterings KGC, Steck S, et al. Tea and cancer prevention: an evaluation of the epidemiologic literature. *Nutr Cancer* 1997;27:1–13
18. Mukhtar H, Katiyar SK, Agarwal R. Green tea and skin-anticarcinogenic effects. *J Invest Dermatol* 1994;102:3–7
19. Weisburger JH, Rivenson A, Garr K, et al. Tea, or tea and milk, inhibit mammary gland and colon carcinogenesis in rats. *Cancer Lett* 1997;114:323–7
20. Suganuma M, Okabe S, Oniyama M, et al. Wild distribution of [3H](-)-epigallocatechin gallate, a cancer preventive polyphenol, in mouse tissue. *Carcinogenesis* 1998;19:1771–6
21. Sadzuka Y, Sugiyama T, Hirota S. Modulation of cancer chemotherapy by green tea. *Clin Cancer Res* 1998;4:153–6

22. Yu R, Jiao JJ, Duh JL, et al. Activation of mitogen-activated protein kinases by green tea polyphenols: potential signaling pathways in the regulation of antioxidant-responsive element-mediated phase II enzyme gene expression. *Carcinogenesis* 1997;18:451–6
23. Jankun J, Selman SH, Swiercz R, et al. Why drinking green tea could prevent cancer. *Nature* 1997;387:561
24. Yang CS. Inhibition of carcinogenesis by tea. *Nature* 1997;389:134–5
25. Fesus L, Szondy Z, Uray I. Probing the molecular program of apoptosis by cancer chemopreventive agents. *J Cell Biochem* 1995;22:S151–61
26. Boolbol SK, Dannenberg AJ, Chadburn A, et al. Cyclooxygenase-2 overexpression and tumor formation are blocked by sulindac in murine model of familial polyposis. *Cancer Res* 1996;56:2556–60
27. Mills JJ, Chari RS, Boyer IJ, et al. Induction of apoptosis in liver tumors by the monoterpene perillyl alcohol. *Cancer Res* 1995;55:979–83
28. Wright SC, Zhong J, Larrick JW. Inhibition of apoptosis as a mechanism of tumor promotion. *FASEB J* 1994;8:654–60
29. Jee SH, Shen SC, Tseng CR, et al. Curcumin induces p53-dependent apoptosis in human basal cell carcinoma cells. *J Invest Dermatol* 1998;111:656–61
30. Jiang MC, Yang-Yen HF, Yen JJY, et al. Curcumin induces apoptosis in immortalized NIH 3T3 and malignant cancer cell lines. *Nutr Cancer* 1996;26:111–20
31. Ahmad N, Feyes DK, Nieminen A-L, et al. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. *J Natl Cancer Inst* 1997;89:1881–6
32. Chen ZP, Schell JB, Ho CT, et al. Green tea epigallocatechin gallate shows a pronounced growth inhibitory effect on cancerous cells but not on their normal counterparts. *Cancer Lett* 1998;129:173–9
33. Fujiki H, Suganuma M, Okabe S, et al. Cancer inhibition by green tea. *Mutat Res* 1998;402:307–10
34. Liang YC, Lin-Shiau SY, Chen CF, et al. Suppression of extracellular signals and cell proliferation through EGF receptor binding by (-)-epigallocatechin gallate in human A431 epidermoid carcinoma cells. *J Cell Biochem* 1997;67:55–65
35. Lin YL, Lin JK. (-)-Epigallocatechin-3-gallate blocks the induction of nitric oxide synthase by downregulating lipopolysaccharide-induced activity of transcription factor nuclear factor- κ B. *Mol Pharmacol* 1997;52:465–72
36. Chan MM, Fong D, Ho CT, et al. Inhibition of inducible nitric oxide synthase gene expression and enzyme activity by epigallocatechin gallate, a natural product from green tea. *Biochem Pharmacol* 1997;54:1281–6
37. Pannala A, Rice-Evans CA, Halliwell B, et al. Inhibition of peroxynitrite-mediated tyrosine nitration by catechin polyphenols. *Biochem Biophys Res Commun* 1997;232:164–8
38. Dong Z, Ma W-Y, Huang C, et al. Inhibition of tumor promoter-induced activator protein 1 activation and cell transformation by tea polyphenols, (-)-epigallocatechin gallate and theaflavins. *Cancer Res* 1997;57:4414–9
39. McCarty MF. Polyphenol-mediated inhibition of AP-1 transactivating activity may slow cancer growth by impeding angiogenesis and tumor invasiveness. *Med Hypotheses* 1998;50:511–4
40. Lu LH, Lee SS, Huang HC. Epigallocatechin suppression of proliferation of vascular smooth muscle cells: correlation with c-jun and JNK. *Br J Pharmacol* 1998;124:1227–37
41. Kennedy DO, Nishimura S, Hasuma T, et al. Involvement of protein tyrosine phosphorylation in the effect of green tea polyphenols on Ehrlich ascites tumor cells in vitro. *Chem Biol Interact* 1998;110:159–72