MINI-REVIEW

Cancer Chemoprevention: Tea Polyphenol Induced Cellular and Molecular Responses

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Abstract

Considerable evidence is now available showing that tea infusions can prevent tumor induction in experimental animals by a variety of chemical carcinogens. Such an action is mainly attributed to the polyphenolic constituets of tea. These polyphenols possess antioxidant activity and interfere with carcinogen activation, show anti-mutagenic and anti-genotoxic properties, exhibit anti-tumor promoting activity and alter certain events in signal transduction pathways. Tea polyphenols are known to exhibit cytotoxicity towards various human tumor cell lines as well as growth inhibition that is accompanied by cell cycle arrest. It has been demonstrated that the cytotoxicity result in inducton of apoptosis. Additionally, tea polyphenols are good candidates for sensitizing tumor cells leading to apoptotic death by cytotoxic drugs.

Key words: Tea polyphenol - catechin - antioxidant - antimutagenic - antigenotoxic - antitumor promotion - apoptosis signal transduction - chemoprevention

Asian Pacific J Cancer Prev, **2**, 109-116

Introduction

Tea from Camelia sinensis L (Theaceae family) is one of the most ancient beverages, consumed by over two-thirds of the world's population. The principal constituents are caffeine, tannins and essential oils. Tannins comprise of a variety of polyphenolic compounds - most important of these are flavonoids called catechins. Tea is classified on the basis of the extent of enzymatic reactions which occur during the manufacture into green tea (non-fermented), black tea (fermented) and paochong or oolong tea (specially treated and semi-fermented). Green tea contains higher amounts of catechin derivatives, such as (-)-epicatechin (EC), (-)-epigallocatechin (EGC) and their gallates (ECG and EGCG). During the production of black tea, some of the catechins are converted to theaflavins (TF) and thearubigins (TR) by enzymatic oxidation and coupling reactions. Catechins and their derivatives are known to contribute towards the flavour of tea while tea aroma is dependent on thr presence of different volatile compounds. Theaflavins (TF) are responsible for briskness and brightness and thearubigins (TR) for color and body or strength (mouth feel). Caffeine is responsible for the stimulating effect of tea and the cancer chemopreventive action of tea is mainly due to its polyphenolic content.

While a protective role of green tea against human cancers is evident from a number of epidemiological studies, the data on black tea are inadequate and limited (Katiyar and Mukhtar, 1996; Kohlmeier et al., 1997; Fujiki et al., 1998; Chen, 1999). It is well known now that tea infusions prevent tumor induction in experimental animals by a variety of chemical carcinogens (see review by Siddiqi and Das, 1999). Such an action is attributed to the polyphenolic content of tea infusions (Stoner and Mukhtar, 1995; Fujiki et al., 1997; Ahmad et al., 1998; Fujiki et al., 1999; Chen, 1999). The catechins ECG and EGCG are the most active agents among the polyphenols (Katiyar and Mukhtar, 1996; Ahmad et al., 1998) whereas EC is the least effective among the four catechins on an equimolar basis (Han, 1997). It is, however, apparent from the available data that the cancer chemopreventive activity of tea is a combined effect of several active components. The action of EGCG in the presence of EC (Suganama et al., 1999), and that of whole green tea infusion shows a more efficient cancer preventive activity than EGCG alone.

The consumption of green tea has also been found to enhance the antitumor activity of sulindac and tamoxifen (Suganama et al., 1999). This helps in reducing the therapeutic doses of these drugs so that the accompanied

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toxic effects. In addition, theanin, an amino acid present in green tea shows similar effect on the action of adriamycin used in the treatment of cancer (Sadzuka et al., 1996; 1998). It has been suggested that green tea extract enhances the effect of antimetabolites in cancer chemotherapy (Zhen et al., 1991). The green tea extracts and EGCG are also known to display anti-metastatic properties (Taniguchi et al., 1992; Sazuka et al., 1995; Fujiki et al., 1999).

Antioxidative Actions

It is well recognized that oxidative stress generates reactive oxygen species that are capable of damaging mammalian cells. The antioxidants and antioxidant enzymes tend to protect cells from such a damage. The phenolic flavonoids are known to have antioxidant activity due to their radical scavenging function (Rafat et al., 1987; Salah et al., 1995). Both green as well as black tea exhibit antioxidative properties due to the polyphenolic content (Xie et al., 1993; Ho et al., 1994; Evans and Miller, 1995; Sarafini et al., 1996; Robinson et al., 1997; Klaunig et al., 1999; Rice-Evans, 1999). It has been shown that green tea infusion, ECG and EGCG markedly retard copper-catalyzed peroxidation of low-density lipoproteins (Yokozawa and Doug, 1997) and also scavenge free radicals responsible for lipid peroxidation in rat heart mitochondria (Hong et al 1994). The tea polyphenols are strong scavengers of superoxide anions and hydroxy radicals (Zhao et al., 1989; Suzuki et al., 1991; Osawa et al., 1990; Okuda et al., 1994). Green tea along with other supplements has also been shown to exhibit scavenging action of reactive oxygen species (Kumari et al., 1996). In addition, the susceptibility of low-density lipoprotein to oxidative modification dramatically improves in presence of tea flavonoids (Ishikawa et al., 1997). EGCG also reduces inflammation-induced generation of peroxynitrate radical and nitrite (Chan et al., 1995). The oxidative damage to DNA generates 8-hydroxy-2´-deoxyguanosine that is used as a plasma or urinary marker for exposure to chemical carcinogens or radiation. The in vivo formation of such DNA-adducts is inhibited by the antioxidants from green or black tea (Xu et al., 1992; Bhimani et al., 1993; Inagake et al., 1995; Fiala et al., 1996; Klaunig et al., 1999; Chung et al., 1999).

The polyphenols from green tea not only show antioxidative action but also exhibit the ability to induce antioxidant enzymes such as glutathione peroxidase, glutathione reductase, catalase, quinone reductase and superoxide dismutase in various tissues (Khan et al., 1992; Yin et al., 1994). These enzymes are known to efficiently quench the oxidative burden minimizing damage to cells.

Effects on Carcinogen Metabolism

It is now well established that procarcinogens are metabolized by cytochrome P-450 containing microsomal monooxygenases (phase I enzymes) to yield highly reactive electrophilic species that react with DNA and other cellular macromolecules involved in the initiation of carcinogenic process. The metabolic activation of carcinogens can be inhibited by a variety of phenolic flavonoids including epicatechins (Firozi et al., 1986; Shah and Bhattacharya, 1986; Bhattacharya and Firozi, 1988; Bhattacharya and Firozi, 1990; Firozi and Bhattacharya, 1995). It has been found that sub-chronic doses of tea induces specific enzymes of the cytochrome P-450 class, including cytochrome P-450 1A1, 1A2 and 2B1, but do not affect other phase I enzymes (Sohn et al., 1994; Bu-Abbas et al., 1994; Chen et al., 1996; Dashwood, 1999). Although the administration of tea extracts accelerates generation of reactive carcinogen metabolites, the products are also detoxified faster as a result of simultaneous induction of phase II enzymes. Thus, oral feeding of green tea polyphenols to mice significantly increased the activity of glutathione S-transferase (Khan et al., 1992; Dashwood et al., 1999) and stimulated hepatic UDP-glucuronosyl transferase activity in rats (Bu-Abbas et al., 1995).

Polyphenols are also known to inhibit the metabolism-dependent formation of DNA adducts by polycyclic aromatic hydrocarbons (Wang et al., 1989). Similarly, the formation of DNA adducts of tobacco specific nitrosamines (Xu et al., 1992) and food-borne carcinogens imidazoquinolines are also inhibited by tea extract and its polyphenols (Xu et al., 1996; Lin et al., 1998). Catechin feeding was found to result in the inhibition of liver microsomal enzymes that are required to activate the hepatocarcinogen aflatoxin B_1 (AFB_1) for the formation of DNA adducts (Aboobaker et al., 1994). The same study also demonstrated catechin induced cytosolic glutathione S-transferase activity that stimulated the formation of specific AFB_1-glutathione conjugate. The formation of carcinogenic heterocyclic amines due to the pyrolysis of proteins during cooking of food can be inhibited by tea and its polyphenols (Weisburger et al., 1994), whereas their activation was found to be suppressed by prepared tea and EGCG (Dashwood et al., 1999).

A major source of human exposure to carcinogenic N-nitroso compounds is through their endogenous formation on nitrosation of secondary and tertiary amines. The tea polyphenols have been shown to inhibit both in vitro and in vivo nitrosation reactions (Stich et al., 1982; Xu et al., 1993) that is believed to occur due to their own nitrosation occurring during the course of such reactions.

Antimutagenic and Antigenotoxic Actions

The antimutagenic activity of tea extracts and polyphenols including ECG and EGCG against various mutagens and carcinogens has been demonstrated using microbial systems (Salmonella typhimurium and Escherichia coli), mammalian cells and in vivo animal tests (for review see Kuroda and Hara, 1999). Using S. typhimurium TA 98

and TA 100, the tea catechins ECG and EGCG have been shown to inhibit the mutagenic activity of direct acting mutagens (Okuda et al., 1984), whereas catechin and epicatechin were found to be inactive (Francis et al 1989a). The extracts of both green and black tea decreased the mutagenic activity of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in E. coli WP2 in a desmutagenic manner. The EGC from green tea leaves and the low molecular weight tannin fraction isolated from black tea extract were also found to exhibit inhibitory effects against the mutagenic activity of MNNG (Jain et al., 1989). The tea extract given orally to rats prior to MNNG was found to significantly reduce the intragastric mutagenic activity of the carcinogen although simultaneous administration showed a reduced effect. The epicatechin was also shown to decrease the metabolism-dependent mutagenicity of AFB_1 in S. typhimurium TA100 but not in TA98, while catechin was ineffective in both strains (Francis et al., 1989b). The antimutagenic activity of several polyphenolic compounds from green tea has been confirmed (Kada et al., 1985; Wang et al., 1989; Mukhtar et al., 1992; Zhao et al., 1992) while TFs from black tea were found to suppress the mutagenicity of H_2O_2 in S. typhimurium TA104 (Shiraki et al., 1994).

Kuroda (1996) demonstrated the inhibitory effects of ECG and EGCG against 6-thioguanine-resistant mutations induced by 4-nitroquinoline-1-oxide in cultured Chinese hamster V79 cells, suggesting that catechins may act in a bio-antimutagenic manner. The tea tannins are shown to be modifiers of induced sister-chromatid exchange and chromosome aberrations in several mutagen-treated cultured mammalian cells (Imanishi et al.,1991). The green tea whole extract suppresses AFB_1-induced chromosome aberrations in bone marrow cells (Ito et al., 1989) and benzo[a]pyrene-induced micronuclei formation in lymphocytes (Sasaki et al., 1993). Catechins were also found to inhibit tobacco-specific nitrosamine-induced DNA single strand breaks in rat hepatocytes (Liu and Castonguay, 1991).

Anti Tumor-promoting Effects

One of the important actions of chemopreventive agents occur through their ability to inhibit tumor promotion. Several tea polyphenols are now known to exhibit significant antitumor promoting activity directly or by inhibiting the action of tumor promoters. Thus, EGCG inhibits tumor promotion by telocidin in 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin tumor in mice (Yoshizawa et al., 1987), while mouse skin tumor promotion by 12-O-tetradecanoylphorbol-13-acetate (TPA) initiated by DMBA was shown to be inhibited by green tea polyphenols (Katiyar et al., 1992). Tea has also been shown to partially block the promotion of DMBA-induced mammary tumorigenesis by high fat diet (Rogers et al., 1998). The suppression of the induced ornithine decarboxylase (ODC), cyclooxygenase and lipoxygenase activities has been suggested to be the possible mode of action by which polyphenols exert their antitumor promoting effect. The topical application of green tea polyphenol fraction resulted in the inhibition of TPA-mediated tumor promotion (Huang et al., 1992) and ODC activity (Huang et al., 1991; 1992). Significant inhibition of TPA-induced epidermal ODC activity by tea polyphenols has also been observed (Wang et al., 1990; Yang et al., 1998). A recent study showed that testosterone-mediated induction of ODC in human prostate carcinoma cell line is significantly suppressed if the cells are pretreated with green tea polyphenols (Gupta et al., 1999). Similar results have been obtained in the ventral prostate of the tea polyphenol-fed rats and mice administered with testosterone, suggesting chemopreventing action of tea polyphenols against prostrate cancer. An enhanced expression of epidermal interleukin-1a mRNA by TPA and its suppression by green tea polyphenols also indicates the anti tumor-promoting effect of these compounds (Katiyar et al., 1995). It has been postulated that EGCG and other compounds in green tea block the interaction of tumor promoters, hormones and growth factors with their receptors, which may account for its observed anti tumor-promoting activity (Komori et al., 1993).

Induction of Apoptosis

Apoptosis or programmed cell death is a normal physiological activity to allow elimination of abnormal cells that are involved in maintaining homeostasis in living system. The life span of both normal and cancer cells is significantly affected by the rate of apoptosis (Fesus et al., 1995). Thus, modulating apoptosis may prove to be an useful approach in the management and prevention of cancer. Black tea polyphenols, green tea extract and EGCG have been shown to inhibit the growth of rat hepatoma, mouse erythroleukemia and the growth of several human cancer cell lines, such as MCF-7 breast carcinoma, HT-29 colon carcinoma, A-427 lung carcinoma and UACC-375 melanoma (Lea et al., 1993; Valcic et al., 1996). The induction of apoptosis by catechins has also been demonstrated in human lymphoid leukemia cells (Hibasami et al., 1996). EGCG also shows the induction of apoptosis and cell cycle arrest in human epidermoid carcinoma cells A-431, human carcinoma keratinocytes HaCaT and human prostrate carcinoma cells DU-145, but not in normal human epidermal keratinocytes (Ahmad et al., 1997). In another study, Chen et al. (1998) demonstrated growth inhibition by EGCG in SV-40 virally transformed human fibroblast cells WI38 through apoptosis but not in normal WI38 cells. In the same study, a differential growth inhibition was observed between a human colorectal cancer cell line Caco-2, a breast cancer cell line Hs-578T, and their respective normal counterparts. Tea polyphenols such as EGCG and ECG also inhibit the growth of human lung cancer cell line PC-9 (Okabe et al., 1997). The study further demonstrated that growth inhibition was accompanied by G2/M phase arrest of the cell cycle (Fujiki et al., 1998). Moreover, the inducing

effect of EGCG on apoptosis has been shown to be enhanced by several cancer preventive compounds such as sulindac and tamoxifen (Suganama et al., 1999). These authors presented substantial evidence that green tea extract is a more effective mixture of polyphenols for cancer prevention than EGCG and that apoptosis being mediated better through enhanced incorporation of tea polyphenols into the cells.

The exposure of human stomach cancer cells KATO III to black tea extracts and TFs resulted in growth inhibition and induction of apoptosis with characteristic DNA fragmentation (Hibasami et al., 1998a). Similar observations were made using green tea extracts and EGCG (Hibasami et al., 1998b). The growth inhibition by various tea polyphenols has been demonstrated in human lung cancer cells H-661 and H-1299, although higher concentrations were needed to produce the effect than were required to achieve similar inhibition in tissues (Yang et al., 1998a; 1998b). Further studies by these authors indicate that tea polyphenols induce production of H_2O_2 that in turn mediates apoptosis leading to the growth inhibition (Yang et al., 1998a).

Role in Signal Transduction

The growth factors and their receptors, families of membrane-associated protein tyrosine kinases (PTK), cytoplasmic serine/threonine protein kinases, G-proteins and nuclear DNA-binding proteins are components of signal transduction pathway involving transmission of messages from the membrane to the nucleus and directing the cells to divide or to differentiate (Cantley et al., 1991). A down regulation of any of these components may transmit the message to the nucleus for fragmentation and eventual apoptosis. EGCG has been shown to interact with the phospholipid bilayer membrane that causes TPA-mediated activation of protein kinase C (PKC), a serine/threonine protein kinase and a key element in the signal transduction pathway (Nishizuka, 1992). In a recent study employing rat aortic smooth muscle cells A7r5, Lu et al. (1998) demonstrated that the membrane bound PTK activity stimulated by serum is significantly inhibited by EGC reducing the levels of many tyrosine-phosphorylated proteins. The EGC also reduced the expression of c-jun mRNA and inhibited phosphorylation of c-jun N-terminal kinase 1 (JNK1). Yu et al. (1997) had also observed considerable activation of mitogen activated protein kinases (MAPK) as well as JNK1 when human hepatoma cells HepG2 were treated with green tea polyphenols suggesting increased mRNA levels of the immediate early genes c-jun and c-fos. Although the implication of these findings is yet unknown, the activation of the MAPK-pathway by tea polyphenols may be a possible explanation for the observed stimulation of the transcription of phase II detoxifying enzymes through antioxidant-responsive element.

The effect of tea polyphenol on the viability of Ehrlich ascites tumor cells and its association with tyrosine phosphorylation has been examined (Kennedy et al., 1998). Although both EGC and EGCG were found to reduce the cell viability, the EGCG showed stimulation of PTK activity. On the other hand, Liang et al. (1997) observed inhibition by EGCG of PTK activities associated with several growth factor receptors in A-431 cells and also showed the blockage of the binding of epidermal growth factor (EGF) to its receptor. These results logically suggest tumor inhibitory effect being mediated through blocking of signal transduction pathways.

The inhibition of EGF- or TPA-induced transformation in a mouse epidermal cell line by EGCG and TFs was found to be associated with inhibition of activated protein-1 (AP-1)-dependent transcriptional activity and DNA binding activity (Doug et al., 1997). The inhibition of AP-1 activation occurs through the inhibition of JNK1-dependent pathway. The downregulation of AP-1, the transcription factor which is an association of the products of protooncogenes fos and jun (Sassone-Corsi et al., 1988) is therefore considered to be a sound therapeutic strategy against cancer (McCarty, 1998).

EGC and EGCG inhibit the inducible NO-synthase (iNOS) activity and block activation of transcription factor NFkb, which is associated with the induction of iNOS (Lin and Lin, 1997). EGCG also inhibited interferon g-activated iNOS and mRNA expression (Chan et al., 1997). EGCG was found to inhibit tumor promoter okadaic acid-induced expression of tumor necrosis factor (TNF) a gene and its release in KATO III cells (Fujiki et al., 1999), PC-9 cells (Fujiki et al., 1998) and in BALB/c-3T3 cells (Suganuma et al., 1996; Suganuma et al., 1999). Since the reduction of TNFa level is the key criterion of cancer preventing agents, it could well be the mode of induction of apoptosis by EGCG.

Prospects for the Future

Although considerable research has been carried out on tea polyphenols and their chemopreventive role against cancer, it is still not fully clear how these compounds exert their action. Therefore, further experimentation is required to ascertain as to how the tea polyphenols block the enzymatic activation of carcinogens or protect DNA from interaction with activated electrophilic metabolites. Since tea polyphenols are unlikely to be effective therapeutic agents against cancer, efforts should be directed to investigate if the polyphenols can sensitize tumor cells to undergo cytotoxic drug- or radiation-induced apoptosis. It is well recognized that several tumor cells are known to be resistant to killing by either radiation or cytotoxic drugs. These cells also exhibit an over expression of certain genes, the products of which such as p21ras and PKC that play an important role in signal transduction pathways. Since the inhibitors of p21ras and PKC are good contenders for reducing tumor cell resistance, it would be vital to examine the effects of tea polyphenols on the suppression of these gene products so

that conventional therapeutic strategy could be made more effective. Chemoprophylaxis by tea polyphenols may, however, continue to be a preferred method of prevention of cancer since no harmful effects of tea drinking have been recognized so far.

Acknowledgement

The authors would like to acknowledge the help received from Ms. Sutapa Chakraborty during the preparation of this article.

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