ANTECANCER MECHANISMS OF POLYPHENOLS DERIVED FROM GREEN TEA

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Abstract

Many studies in different cell lines, animal models and human epidemiological trials suggest a protective role of dietary polyphenols against different types of cancers (Watson, et al., 2000; Wenzel et al., 2000; Yang et al., 2001). Clinical trials have correlated polyphenolic intake with prevention of particular cancers, showing a decreased risk for different types of cancers (Knekt et al., 1997; Key et al., 1999; Arts et al., 2002; Su and Arab, 2002) or a diminished recurrence of cancer (Nakachi et al., 1998; Le Marchand et al., 2000) after the consumption of polyphenols or certain foods or drinks, such as tea and red wine, rich in these phenolic compounds. The combination of green tea extract or green tea catechins and anticancer compounds has been paid more attention in cancer treatment. Previous studies demonstrated that the combination of chemotherapeutic drugs and green tea extract or tea polyphenols could synergistically enhance treatment efficacy and reduce the adverse side effects of anticancer drugs in cancer patients. Tea derived from the leaves and buds of Camellia sinensis (Theaceae) is consumed worldwide. In this review, we summarize the experimental evidence regarding the effects of green tea-derived polyphenols in conjunction with chemotherapeutic drugs on anti-tumor activity, toxicology, and pharmacokinetics. We believe that the combination of multidrug cancer treatment with green tea catechins may improve treatment efficacy and diminish negative side effects. Two major action mechanisms of (-)-epigallocatechin gallate have been proposed; one associated with its anti-oxidative properties and the other with its pro-oxidative activity. When reactive oxygen species are assumed to be involved, our findings that (-)-epigallocatechin gallate downregulated hepatocyte nuclear factor-4α, sterol regulatory element-binding proteins, and tumor necrosis factor-α may explain the anti-cancer effect of green tea as well. However, further studies are required to elucidate which determinant directs (-)-epigallocatechin gallate action as an anti-oxidant or a pro-oxidant for favorable activity.

Keywords: Green tea, catechin, epigallocatechin gallate, cancer, reactive oxygen species tea polyphenol, anticancer agent, synergistic anticancer activity, toxicology, pharmacokinetics.

Introduction

Carcinogenesis in humans is a multistage process involving a series of events and generally occurs over an extended period. During this process, accumulation of genetic and epigenetic alterations leads to the progressive transformation of a normal cell into a malignant cell. Cancer cells acquire several abilities that most healthy cells do not possess: they become resistant to growth inhibition, proliferate without dependence on growth factors, replicate without limit, evade apoptosis, and invade, metastasize, and support angiogenesis (Hanahan and Weinberg, 2000). It is currently accepted that diet can affect the overall process of carcinogenesis in different ways. Its constituents may contain cancer causing substances but can
also contain The American Cancer Society in its recent annual report, “Cancer Statistics, 2012”, estimates approximately 1.64 million new cancer cases to be diagnosed and nearly 577,000 mortalities from cancer projected to occur in USA alone in the year 2012 (Siegel et al., 2012). Despite being one of the major causes of death across the world, cancer has been shown to be a largely preventable disease, highly susceptible to modulation by dietary factors. Dietary patterns, foods, nutrients and other dietary constituents are closely associated with the risk for several types of cancer, and in this regard, it has been estimated that 35% of all cancers can be prevented through appropriate dietary modifications (Doll and Peto, 1981; Manson, 2003). The biologically active chemicals present in fruits, vegetables and grains are termed as phytochemicals, many of which provide desirable health benefits beyond nutrition to reduce the risk of a number of chronic diseases (Liu, 2003). It is believed that phytochemicals have the ability to modify the disease process thus relating the food stuffs, beyond their basic nutritional benefits, to disease prevention (Roger et al., 1993; Thomasset et al., 2007). Such foods have also been termed as ‘functional foods’. Thus, convincing evidence suggests that a change in dietary behaviour such as increasing the consumption of fruits and vegetables is a practical strategy for significantly reducing the incidence of chronic diseases. Green tea was first brought to Japan, more than 1000 years ago, from China as a form of medicine. In 1211, the Japanese Zen monk Eisai published a book entitled “Kissa Youjouki” which means “promotion of health by tea”, and described that “tea is a marvelous preventive medicine to maintain people’s health and has an extraordinary power to prolong life”. This paper mainly reviewed the experimental data regarding the effects of tea polyphenols in conjunction with chemotherapeutic drugs on anti-tumor activity, toxicology, and pharmacokinetics. We believe that the combination of green tea catechins and anti-cancer drugs may enhance cancer treatment efficacy and diminish negative side effects.

**Cancer chemoprevention and dietary polyphenols**

Fruits and vegetables contain a wide variety of phytochemicals that are regarded as effective protective agents. One such prominent class of phytochemicals, plant derived foods and beverages are rich in, are dietary polyphenols that have received much attention over the last two decades for their health benefits, including cancer chemopreventive effects. Polyphenols are plant secondary metabolites that serve as a component of plant defense mechanisms against predation by microorganisms, insects and herbivores.

They are widely distributed plant derived dietary constituents and have been implicated as the active components in a number of herbal and traditional medicines (Wollenweber, 1988). Polyphenols are known to possess a wide range of pharmacological properties including cardioprotective, neuroprotective, anti-inflammatory and anticancer properties (Szewczuk et al., 2004; Dai et al., 2006; Thomasset et al., 2007; Ullah and Khan, 2008).
Synergistic Anticancer Activity of Tea Polyphenols and Chemotherapeutic Agents

The combination of green tea catechins and anticancer drugs is a new treatment strategy that has been widely accepted by cancer researchers [11]. Although anticancer drugs and tea polyphenols are very different in terms of structure and function, tea polyphenols can synergistically enhance the effects of anticancer drugs and make them 10–15 times more effective than monotherapy [11]. Some studies have also reported beneficial effects of EGCG or green tea extract with anticancer drugs, such as bleomycin, cisplatin, tamoxifen, and bortezomib [16–19]. We have also studied the effect of green tea extract on 5-fluorouracil (5-FU) in cancer cells and animals. Our results demonstrated that green tea catechins with anticancer agents
are more effective than monotherapy [15]. The effects of tea polyphenols or tea extracts on the therapeutic efficacy of anticancer agents are listed in Table 1.

- Combination of Tea Polyphenols and Bleomycin
- Combination of Tea Polyphenols and Cisplatin
- Combination of Tea Polyphenols and Ibuprofen
- Combination of Tea Polyphenols and Tamoxifen
- Combination of Tea Polyphenols and Bortezomib
- Combination of Tea Polyphenols and Other Anticancer Drugs

Table 1. The effects of green tea catechins on anticancer compounds in anti-tumor activity.

<table>
<thead>
<tr>
<th>Anticancer Drugs</th>
<th>Experiment</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>SiHa cervical cancer cells or uterine cervical cancer cells were treated with tea polyphenol and bleomycin; poly-caspase activity, early apoptosis, and the expression of caspase-3, caspase-8, caspase-9, Bcl-2, and p53 were assessed.</td>
<td>Synergistic increase in antitumor effects.</td>
</tr>
<tr>
<td>5-Fluorouracil (5-FU)</td>
<td>Some cancer cells—such as human SW480, BIU-87, BGC823, and Hep3B—were treated with green tea and 5-FU; the cytotoxicity, cell apoptosis, and proliferation were studied.</td>
<td>Increase in cell apoptosis; synergistic inhibition of cell proliferation; no reduction in antitumor activity.</td>
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<tr>
<td>Cisplatin</td>
<td>Cancer cells YCU-NB61, YCU-H891, Hep3B, SW480, BIU-87, BGC823, et al. were coadministered cisplatin with tea polyphenols; the cell apoptosis and proliferation were studied.</td>
<td>Synergistic inhibition of cell proliferation; induction of apoptosis.</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>DU-145 cells were treated with EGCG and ibuprofen; cell death analysis, immunoblotting, RT-PCR analysis, and caspase activity assay were used.</td>
<td>Synergistic effect on the anti-proliferative and pro-apoptotic action.</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Cancer cells PC-9, MCF-7, and MDA-MB-231 were treated with tea polyphenols and tamoxifen; some factors such as EGFR, MMP-2, MMP-9, and EMMPRIN were assessed.</td>
<td>Induction of apoptosis; enhanced expression of apoptotic genes; synergistic increase in antitumor effects.</td>
</tr>
<tr>
<td>Sulindac</td>
<td>PC-9 cancer cells were treated with sulindac and tea polyphenols; gene expression was assessed.</td>
<td>Induction of apoptosis; enhanced expression of apoptotic genes.</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Cancer cells 26S and CWR22 were treated with bortezomib and tea polyphenols; cell apoptosis and proliferation were assessed.</td>
<td>Antagonized antitumor activity.</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>A549 and MCF-7 cancer cells were treated with celecoxib and tea polyphenols; the cell activity and gene expression were assessed.</td>
<td>Increased cell apoptosis;enhanced expression of GADD153 gene.</td>
</tr>
<tr>
<td>Luteolin</td>
<td>Cancer cells H292, A549, H460, and Tu212 were treated with luteolin and EGCG; phosphorylation of p53 was studied.</td>
<td>Induction of caspase-8 and caspase-3 cleavage; increase in cell apoptosis.</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>PC-3ML cancer cells were treated with docetaxel and tea polyphenols; hTERT and Bcl-2 were studied.</td>
<td>Increase in the expression of apoptotic genes; reduction in growth rate of cancer cells.</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Cancer cells PC-9, A549, NCI-H460, and ER alpha-breast cancer cells were treated with curcumin and tea polyphenols; the cell activity and cell cycle were assessed.</td>
<td>Induction of apoptosis; enhancement of cell cycle arrest at G1 and S/G2 phases.</td>
</tr>
</tbody>
</table>
Combination of Caffeine and Anticancer Drugs

Ameliorating Toxicity Induced by Chemotherapeutic Agents

Antioxidants may protect against chemotherapy-induced toxicity. Due to their antioxidant and ROS-scavenging properties, green tea polyphenols could circumvent the adverse effects of ROS and chemotherapy and enhance treatment efficacy (Table 2). Additionally, P-glycoprotein (P-gp) plays an important role in multidrug resistance. EGCG was found to inhibit the transport activity of P-gp and may be an effective P-gp modulator. EGCG also increased chemotherapy drug accumulation in multidrug resistant cells. Treatment with green tea ameliorated the cardiotoxicity of doxorubicin. Doxorubicin-induced oxidative stress, heart and liver morphological changes, and metabolic disorders were also mitigated by green tea in male Wistar rats. The mechanism underlying these effects is currently unknown, but it may involve the modulation of enzymes required for lipid synthesis, such as HMG-CoA (3-hydroxy-3-methylglutary-coenzyme A) reductase. Two major problems in cancer chemotherapy are adverse side effects and multidrug resistance. Chemotherapy can cause fatigue, nausea, vomiting, and more serious side effects in cancer patients. Previous studies found that anticancer drugs caused serious adverse effects via antioxidant defense abnormalities against reactive oxygen species (ROS).

Table 2. A combination of green tea catechins and anticancer compounds ameliorating the toxicity induced by chemotherapeutic agents.

<table>
<thead>
<tr>
<th>Anticancer Drugs</th>
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<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Wistar albino rats with cardiotoxicity induced by doxorubicin were treated with green tea. AST, CK, LDH, LPO, cytochrome P450, blood glutathione, tissue glutathione, and enzymatic and non-enzymatic antioxidants were evaluated along with histopathological studies.</td>
<td>Oral administration of green tea prevented doxorubicin-induced cardiotoxicity by accelerating heart antioxidant defense mechanisms and downregulating the LPO levels to the normal levels.</td>
</tr>
<tr>
<td>Doxorubicin (DOX)</td>
<td>Neonatal Rats with cardiotoxicity induced by doxorubicin were treated with EGCG; LDH, MnSOD, catalase, and glutathione peroxidase were detected.</td>
<td>EGCG could protect cardiomyocytes from DOX-induced oxidative stress by attenuating ROS production and apoptosis, and increasing activities and protein expression of endogenous antioxidant enzymes.</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Rats were treated with doxorubicin and different doses of EGCG. Cardiac enzymes (creatine kinase isoenzyme-MB and lactate dehydrogenase) and histopathological changes were studied.</td>
<td>EGCG possesses cardioprotective action against doxorubicin-induced cardiotoxicity by suppressing oxidative stress, inflammation, and apoptotic signals, as well as the activation of pro-survival pathways.</td>
</tr>
</tbody>
</table>
Effects of green tea on TNF-α

TNF is a proinflammatory cytokine. Fujiki and his coworkers have demonstrated that the anti-cancer effect of green tea can be correlated with inhibitory effect on gene and protein expression of TNF-α (Suganuma et al., 2000). Our animal experiment using galactosamine-induced hepatitis model rats showed the consumption of green tea beverage with a high content of EGCG attenuated. The effect was correlated with the beverage’s inhibition of the gene and protein expression of inflammatory cytokines, TNF-α and interleukin 1β. Similarly, EGCG reduced the mRNA levels of TNF-α and interleukin-1β in the mesenteric adipose tissue of non-obese type 2 diabetic rats when they were given a diet containing 0.1% EGCG for 25 weeks. These finding are compatible with the result of a human clinical study demonstrating that GTE caused reduction in serum levels of TNF-α and C-reactive protein (Bogdanski et al., 2012).

Anti-cancer effects of green tea.

Most of cellular and animal experiments have demonstrated the anti-cancer effects of green tea and EGCG (Yang et al., 2009; Khan and Mukhtar, 2010; Singh et al., 2011; Yang and Wang, 2011; Suzuki et al., 2012; Khan and Wang, 2013; Miyoshi et al.). The major compound contributing to the activity of green tea is believed to be EGCG. Human epidemiological and intervention studies have also shown that green tea and tea catechins exert preventive effects against various cancers. On the other hand, many findings have failed to demonstrate such effects. These conflicting results may arise from several confounding factors, including the methods of quantifying tea consumption, tea temperature, cigarette smoking, alcohol consumption, and the differences in genetic and environmental factors such as race, sex, age, and lifestyle.

Conclusions

The benefits of combining tea polyphenols with anticancer compounds are now widely
accepted by cancer researchers. Previous studies have demonstrated that a combination of chemotherapeutic drugs and green tea extract could enhance therapeutic effects and reduce the adverse side effects of anticancer drugs most of the time. Several papers have also reported the potential for negative interactions between tea polyphenols and anticancer drugs. In this article, we provided a brief overview of the pharmacodynamics, toxicology, and pharmacokinetic interactions between green tea and anticancer drugs. We believe that the combination of green tea and anticancer drugs may be important in enhancing therapeutic efficacy while diminishing negative side effects. Most of the pharmacological properties of plant polyphenols are considered to reflect their ability to scavenge endogenously generated oxygen radicals or those free radicals formed by various xenobiotics, radiation etc. However, some data in the literature suggest that the antioxidant properties of the polyphenolic compounds may not fully account for their chemopreventive effects (Gali et al., 1992; Hadi et al., 2000). Although most plant polyphenols are considered to have a physiological role as antioxidants, they may also exhibit prooxidant properties in the presence of transition metals such as copper (Ahmad et al., 1992; Inoue et al., 1994). The results presented in this chapter lead to the conclusions that all the three flavones tested, namely luteolin, apigenin and chrysin, (i) are able to interact with DNA as well as Cu(II) and possibly form a ternary complex of DNA-Cu(II)-flavone; (ii) are able to reduce Cu(II) to generate Cu(I); (iii) cause redox cycling of copper leading to the generation of various reactive oxygen species, particularly the hydroxyl radical, (iv) are able to induce strand scission in plasmid DNA and calf thymus DNA in the presence of copper ions; (v) show a similar copper dependent activation leading to enhanced DNA degradation in a cellular system of human peripheral lymphocytes; and (vi) mobilize nuclear, possibly chromatin bound copper in the DNA breakage reaction. These observations suggest that such a prooxidant mechanism of DNA breakage involving flavone-Cu(II) system is physiologically feasible and could be of biological significance. These results place the flavones luteolin, apigenin and chrysin among the other classes of plant derived polyphenolic antioxidants such as isoflavones (Ullah et al., 2009), anthocyanidins (Hanif et al., 2008), stilbene (Azmi et al., 2006), catechins (Azam et al., 2004), curcumin (Ahsan and Hadi, 1998) and tannins (Bhat and Hadi, 1994), which also exhibit prooxidant DNA damaging properties in the presence of copper ions. Previous studies on polyphenols from this laboratory have shown that a ternary complex of DNA, Cu(II) and polyphenol is formed which generates oxygen radicals in situ via Cu(I) (Rahman et al., 1989).

References:


herbal medicine and combination cancer prevention study with EGCG and sulindac or tamoxifen. Mutat. Res. 2003, 524, 119–125. [CrossRef]


