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Review

Molecular aspects of cancer chemopreventive and therapeutic efficacies of tea and tea polyphenols

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ABSTRACT

The natural dietary product tea (*Camellia sinensis*) and its bioactive polyphenols such as epigallocatechin gallate (EGCG) and theaflavin (TF) demonstrated potential anticancer effects in different preclinical and clinical studies. The aim of the present review was to understand the molecular mechanisms of the tea and tea polyphenol-mediated cancer prevention and therapy. In the setting of in vivo cancer prevention studies, administration of the tea and tea polyphenols at preinitiation stages only showed partial prevention, whereas continuous administration showed potential effect in restriction of carcinogenesis in the body's multiple organs at early premalignant stages throughout the experiment. Similar to different in vitro cancer cell models, treatment after initiation stages showed potential therapeutic efficacy in vivo. But, the mechanisms of prevention and therapy were found to be similar regardless of tea and its polyphenols. They mainly serve as antioxidants and induce the detoxification system, thereby inhibiting carcinogen metabolism and cancer initiation. Additionally, they could inhibit self-renewal, proliferation, and survival of the tumor-initiating population in restriction of the carcinogenesis progression from cancer initiation and promotion. This might be a result of the modulation of membrane organization, interaction with DNA/RNA/proteins and epigenetic modifications, as well as regulation of cellular replicative potential by the tea polyphenols.

Introduction

Despite the advancement in cancer research over the past decades, the disease remains one of the leading causes of mortality worldwide and we are learning to live against cancer [1]. Several studies based on in vivo animal models and pathologic analysis of human neoplasm revealed that carcinogenesis is a multistage process involving predisposition of genetic alterations that drive progressive transformation of a normal stem cell to tumor-initiating clones or cancer stem cells (cancer initiation) and causes an irreversible progression of the process (promotion) to form malignant neoplasms and invade adjacent tissues [2,3]. Studies suggested that prevention of the neoplastic transformation of stem cells by changing different environmental, lifestyle factors, or both, would be a better prospect in the reduction of cancer risk [3]. Simultaneously, early detection and treatment with increased sensitivity of the transformed clones are the most promising and feasible means of cancer therapy [3].

Many natural compounds, beverages, and dietary constituents at nontoxic doses showed anticancer activities [4,5]. Among them tea, derived from the dried leaves of the *Camellia sinensis* plant, is a major source of dietary flavonoids (or polyphenols) and is consumed by a large portion of the world's population [6,7]. Depending on tea processing, different types of tea are available. Among the various teas, green and black teas are used widely [7]. Green tea and its catechins [(−)-epigallocatechin-3-gallate (EGCG), (−)-epigallocatechin (EGC), (−)-epicatechin-3-gallate (ECG), and (−)-epicatechin (EC)] inhibit tumorigenesis at a number of organ sites [7]. EGCG is the most potent and is predominantly credited with much of the cancer-preventive and therapeutic effects of green tea [6,7]. Black tea is very popular. The catechins in black tea are oxidized or condensed to theaflavins (TFs) (TF, TF-3-gallate, TF-3′-gallate, and TF-3-3′-digallate) and thearubigins (TRs) [6,7]. Although,

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green tea is best studied for its health benefits, emerging data is showing that black tea and its polyphenols may possess similar health-promoting attributes and anticancer effects in laboratory models [6,7]. A number of potential mechanisms of the tea and its polyphenols have been proposed and more or less similar functions have been evident in cancer prevention and therapy. But, how tea polyphenols exert multiple biological roles in restriction of multiple cancers is not clearly known. For this purpose, the present review discusses the cancer-preventive and therapeutic roles of green and black teas and their polyphenols (EGCG/TF) especially on in vivo carcinogenesis models. We focused on possible molecular mechanisms behind the prevention and therapy. Thus, the review may have wide implications on cancer prevention and therapy, which may have importance not only in cancer treatment but also may be applicable to studies of other dietary materials.

Tea and tea polyphenols in cancer prevention and therapy

Different epidemiologic studies demonstrated that daily consumption of tea (≥4 cups) might prevent the risk for different human cancers such as skin, oral, lung, breast, stomach, pancreatic, ovarian, and prostate cancers associated with tobacco habit or alcohol consumption [7–9]. However, these studies encountered several parameters such as variation in cancer etiology in different populations, difficulties in quantification of tea consumption, and low bioavailability of the polyphenols [5]. Experiments in animal models were performed extensively to understand the cancer-preventive and therapeutic roles of the tea and its polyphenols. First demonstration of the chemopreventive effect was evident on a mouse skin carcinogenesis model [10]. Later pretreatment or continuous administration (preventive group), as well as administration at postinitiation stages (therapeutic group), of the tea infusion and its active polyphenols mainly EGCG and TF through various routes (mainly oral gavage) showed potential anticarcinogenic effects in animal models (Table 1). The doses for the tea and tea polyphenols were selected based on toxicity analysis. These studies included primary carcinogenesis model of skin, oral, esophagus, mammary, lung, stomach, liver, pancreas, colon, and intestine, as well as different multiorgan models where tea and tea polyphenols showed potential cancer-preventive and therapeutic effects (Table 1). In the setting of cancer prevention studies, histopathologic analysis demonstrated that treatment before initiation stages (pretreatment) only resulted in partial chemoprevention, whereas continuous treatment showed a better preventive effect with restriction of carcinogenesis at early premalignant stages throughout the experimental periods (Fig. 1). This indicates that pretreatment might be effective at certain time points, whereas a continuous tea habit might inhibit expansion of tumor-initiating clones in early dysplastic stages for all experimental periods, resulting restriction of the carcinogenesis progression. Treatment at postinitiation stages restricted the carcinogenesis from higher stages to lower dysplastic stages, indicating the importance of the tea and tea polyphenols in cancer therapy (Fig. 1). Similarly, in multiorgan carcinogenesis models the tea and tea polyphenols prevented carcinogenesis in multiple organs in the same animal system, showing potential roles in cancer prevention and therapy in several organs at a time (Table 1). The therapeutic efficacy also was validated on several cancer cell lines such as skin, oral, lung, breast, liver, pancreas, colon, and prostate [32,33]. Importantly, the mechanisms of the preventive and therapeutic efficacies of the tea and tea polyphenols were found to be similar. Depending on the time of administration (i.e., before or after initiation stages of the carcinogenesis) the tea and tea polyphenols showed preventive or therapeutic effects. Table 1 summarizes the effect and mechanisms of tea and tea polyphenols on cancer prevention and therapy.

Molecular mechanism of cancer prevention and therapy by tea and its polyphenols

The biological activity of the tea is attributed by tea polyphenols [7]. In different animal carcinogenesis models, tea polyphenols showed potential antioxidative effects and induced activity of different detoxification enzymes including glutathione *S*-transferase (GST), UDP-glucuronyl transferase, glutathione peroxidase (GPx), superoxide dismutase, and catalase (CAT), resulting in inhibition of carcinogen activation and cancer initiation (Table 1). Studies showed that tea polyphenols could inhibit stem cell population (like CD44-positive population) and their self-renewal (*Wnt*/β-catenin and *Hedgehog/Gli1* pathways), modulate different key regulatory genes of downstream signaling events of the self-renewal pathways like with cell cycle (*cMyc, Cyclin D1, p21*, etc.), signaling (*EGFR, hRas, ERK1/2, NF-kβ, Nrf2*, etc.), angiogenesis (*VEGF*), epithelial-to-mesenchymal transition (*E-cadherin*), and apoptosis (*p53, Bax, Bcl2, Caspase 3,* etc.) in restriction of carcinogenesis progression at early premalignant stages from cancer initiation or promotion (Table 1).

Studies showed cellular uptake of tea polyphenol EGCG in different normal and cancer cells depending on dose and time of incubation [34–39]. It was evident that fluorescein isothiocyanate (FITC)-conjugated EGCG (FITC–EGCG; 65 μM/L) could accumulate at the membrane within 30 min and after 1 h it could be detected in the cytoplasm and nucleus of mouse fibroblast cells [34]. In the case of normal human fibroblast, FITC–EGCG (100 μM/L) could enter into cells after 4 h and could be detected in cytoplasm and nucleus after 24 h [35]. In the case of human fibrosarcoma cells, FITC–EGCG was detected in the membrane after 2 h and after 12 h it could be detected in the cytoplasm and nucleus [36]. Similarly, H3-labeled EGCG could be detected in the membrane, cytoplasm, and nucleus of human colon carcinoma, lung carcinoma cells, and in mitochondria of rat cerebellar granule neurons [37–39]. How tea polyphenols could enter into cells and regulate multiple biological processes at a time during cancer prevention and therapy is discussed in several in vitro cancer cell line–based studies that proposed molecular mechanisms of the tea polyphenols in this regard. The studies are discussed next and summarized in Figure 2.

Antioxidation and activation of detoxification system

The polyphenolic structure might be responsible for antioxidation and activation of the detoxification system [9,40]. The polyphenols showed free radical scavenging activity and chelate metal ions such as iron and copper, thereby preventing redox-active transition metals from catalyzing free radical formation [9,40]. Thus, generation of reactive oxygen species such as nitric oxide, nitrogen dioxide, and peroxynitrite were found to be inhibited by tea polyphenols [9]. Tea polyphenols, mainly EGCG, could reduce oxidative stress and decrease levels of lipid peroxidation, protein carbonylation, plasma-oxidized low-density lipoprotein, plasma hydrogen peroxide, C-reactive protein, several proinflammatory cytokines, and oxidative DNA damage [5,8,11,18,40,41]. They also could increase detoxification