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Black tea in chemo-prevention of cancer and other human diseases

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Abstract

Tea is the most popular functional beverage in the world and has been gaining more and more attention for its health beneficial properties. Among common teas, black tea is consumed more than green tea and oolong tea worldwide. Numerous studies have shown the biological activities of black tea and its polyphenols that include anti-oxidant, anti-tumor, anti-inflammation and metabolic regulation. Tea polyphenols such as theaflavins and catechins are considered to be multifunctional compounds that could be effective in the prevention or treatment of various cancers, cardiovascular disease, chronic inflammation, obesity, metabolic syndrome, and neurodegenerative diseases. In this review, we summarized the up-to-date research and underlying molecular mechanisms of black tea and its polyphenols.

Keywords: Black tea; Theaflavins; Catechins; Human disease; Molecular mechanism; Cancer

1. Introduction

As tea drinking has become part of a phenomenal global culture nowadays, it is mainly attributed to its biological functionality in contrast to the traditional tea drinking, which is mostly driven by its flavor and stimulant effect. Indeed, polyphenolic compounds in tea have many health promoting activities due to their diverse biological actions including antioxidant, anti-inflammatory, anti-tumor and metabolic regulatory effects that could lead to cancer prevention and protect against metabolic, cardiovascular and inflammatory diseases.

Since black tea consumption accounts for 78% of the overall tea beverage industry [1], we directed our attention to the studies of black tea in both its chemistry and biological activities. In our previous review, we focused on the chemistry of black tea: the formation, composition, analysis and stability of black tea [1]. From the reported data and our analysis, we concluded that the major polyphenols in black tea are composed of theaflavins (Table 1) and catechins (Table 2). Black tea is different from other tea such as green tea, white tea and oolong tea not only in their processing and flavor, but also in their chemical compositions. Chemical analysis showed that black tea also contains high amount of green tea catechins in addition to theaflavins. Therefore, both catechins and theaflavins contribute to the bioactivity of black tea either by additive and/or synergistic effects.

Numerous articles have summarized the biological properties of green tea and its catechins and a few have reviewed bioactivity of black tea in general. However, few articles have attributed the bioactivity data of black tea to its chemical profiles. In this review, we summarized the health beneficial properties of black tea and also listed the bioactivities of individual theaflavins (TFs), the key identity marker of black tea. By describing various health promoting effects of black tea and the potential mechanisms from its major ingredients, we would like to advocate the importance of chemical profiling in natural product research and functional food products development.

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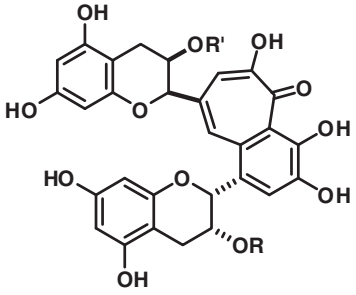
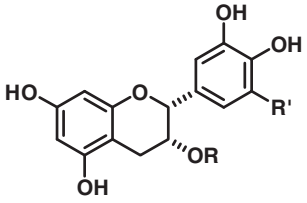
Table 1
Chemical structure of theaflavins.



Compound	R	R′
Theaflavin (TF1)	H	H
Theaflavin-3-monogallate (TF2a)	Galloyl	H
Theaflavin-3′-monogallate (TF2b)	H	Galloyl
Theaflavin-3,3′-digallate (TF3)	Galloyl	Galloyl

Table 2
Chemical structure of catechins.



Compound	R	R′
Epicatechin (EC)	H	H
Epigallocatechin (EGC)	H	OH
Epicatechin gallate (ECG)	Galloyl	H
Epigallocatechin gallate (EGCG)	Galloyl	OH

2. Cancer prevention and anti-tumor effects of black tea

Cancer is the most common cause of human mortality worldwide. Cancer cells are capable of limitless replication potential due to their self-sufficient growth signals and their resistant to anti-growth signals from host defense that enable them to evade apoptosis. Furthermore, they can sustain angiogenesis that can lead to tissue invasion and metastasis [2]. Targeting the regulation of key molecules and cellular signaling pathways in tumorigenesis by natural products was effective in preventing or reducing risk of cancer [3]. There are many reports on the efficacy of the anti-tumor and cancer prevention activity of black tea. For instance, studies from Baker et al. [4] and Doral et al. [5] support the cancer chemo-preventive effect of black tea in the development of prostate cancer, ovarian cancer and rectal cancer. However, others [6,7] do not. The discrepancy of the effects could be a result of actual dosage differences among studies with unspecified amount ingestion of bioactive tea polyphenols. Daily consumption of black tea in women lowered the concentration of 17β-estradiol (E2), which may reduce hormone-related cancer risk [8] (Table 3). Regular black tea consumption is also associated with the reduced risk of ovarian and bladder cancer in female subjects [9–11]. Furthermore, several research groups have attempted to elucidate the molecular mechanisms of black tea and its polyphenols.

Drinking black tea reduced incidence and number of skin papilloma in 7,12-dimethylbenz[a]anthracene (DMBA)-treated mice through activation of detoxification enzymes and decreased lipid peroxidation [12]. Oral administration of black tea polyphenols delayed tumorigenesis, reduced tumor number and volume in DMBA-induced mouse skin carcinogenesis through induction of apoptosis in tumor cells [13]. Topical application of combined black tea polyphenols and resveratrol synergistically inhibited DMBA/TPA-induced skin carcinogenesis by reducing tumor incidence, number and volume. Mechanistic study showed that this combination down-regulated mitogen-activated protein kinases (MAPKs) and increased tumor suppressor gene *p53* and apoptosis [14]. Consistent with the results in skin cancer model, oral intake of black tea polyphenols or extract also suppressed DMBA-induced mammary tumors and oral tumors by scavenging reactive oxygen species (ROS) that reduced the oxidative stress [15] and down-regulating cyclyoxygenase-2 (COX-2), nuclear factor kappa-B (NF-κB) and protein kinase B (Akt) [15], and interfering with the activity of carcinogen metabolizing enzymes [16].

In DMH (1,2-dimethylhydrazine)-induced colorectal tumor model, consumption of tea with high content polymeric black tea polyphenols inhibited the tumorigenesis *via* down-regulation of Wnt/β-catenin pathway and proliferative gene expression [17]. Oral administration of black tea polyphenols was also effective against arsenic-induced formation of 8-hydroxy-2′-deoxyguanosine (8-OHdG) through up-regulation of DNA repair enzymes in Swiss albino mice [18].

One common feature in the effects of black tea in antagonizing various chemical-induced carcinogenesis is the activation of the detoxification enzymes. The detoxifying enzyme system plays an important role in determining the final fate of carcinogens/procarcinogens and their subsequent impact on carcinogenesis [19]. Regulation of many detoxifying enzymes is mediated by the transcription factor nuclear factor E2-related factor 2 (Nrf2) that binds to the antioxidant response element (ARE)/electrophile response element (EpRE), which is located in the promoter region of related genes to initiate gene expression. Ingredients in black tea including EGCG activate Nrf2 and up-regulate the protective enzymes [19,20]. In addition to Nrf2 activation, there are many other important mechanisms that contribute to the anti-carcinogenic effects by black tea polyphenols.

Theaflavins (TFs) are major bioactive components in black tea and are classified as theaflavin (TF1), theaflavin-3-*O*-gallate (TF2a), theaflavin-3′-*O*-gallate (TF2b) and theaflavin-3,3′-*O*,*O*-digallate (TF3) (Table 1). TFs' treatment of human leukemic U937 and K562 cells suppressed Akt signaling, thus blocked Wnt/β-catenin signaling, cyclin D1 level and increased levels of FOXO1 and p27 that contribute to induce G0/G1 cell-cycle arrest [21]. In HeLa cervical cancer cells, TFs caused apoptosis by generation of ROS, increase of p53 and down-regulation of COX-2 and cyclin D1 *via* blockage of Akt and NF-κB activation [22].

While some of the actions may come from the combinations of TFs, an individual TF has its individual activities against cancer cells. TF1 induced ROS-mediated apoptosis