Green Tea Catechins - Pharmacokinetic Properties and Health Beneficial Effects

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Abstract

In this review, we provide information on the pharmacokinetic properties of green tea catechins and their beneficial health effects. The major catechins in green tea are (-)-epicatechin (EC), its hydroxyl derivative (-)-epigallocatechin (EGC), and their gallic acid esters, (-)-epicatechin-3-gallate (ECg) and (-)-epigallocatechin-3-gallate (EGCg). We developed an analytical method for determination of the presence of green tea catechins in human serum using ion-pair HPLC with electrochemical detection to estimate the pharmacokinetic parameters of target catechins. The Cmax values indicated that catechin absorption was relatively low. One of the gallated catechins, EGCg, had a longer half-life than the non-gallated catechins. Green tea catechins, in particular, have attracted attention as cancer preventive agents in terms of their low toxicity and being readily available to the general population. Several epidemiological studies revealed that green tea consumption reduces cancer incidence. Numerous in vitro cell culture studies have shown that EGCg, which is defined as a major green tea catechin contributing to green tea’s anticancer effects, inhibits cell growth concomitant with induction of apoptosis. We have previously found that the cell death-inhibiting gene, Bcl-xL, was decreased by EGCg. These results support the hypothesis that EGCg regulates cytoplasmic NF-κB and subsequently induction of apoptosis. Green tea consumption may also play a role in preventing other lifestyle diseases, such as cardiovascular diseases and stroke, due to its hypocholesterolemic and hypotensive activities. In conclusion, habitual green tea drinking may promote human health by preventing lifestyle-related diseases.

Introduction

The tea plant (*Camellia sinensis*), a native of southern China, has been known for more than two thousand years in Chinese botany and medicine. Lu Yu, who lived from 733 to 804, is respected as the Sage of Tea for his contributions to Chinese tea culture. He is best known for his seminal book, *Ch’i-a Ching*, or The Classic of Tea, the first definitive work on the cultivation, preparation, and drinking of tea. Eisai (1141-1215) was a Japanese Zen Buddhist monk who, after studying in China, brought back new tea seeds and introduced the tea ceremony. He also wrote the first book about the health benefits of drinking green tea, ‘*Kissa- Yohjoh-Ki*’ (Maintaining Health by Drinking Tea). Sen Rikyu (1522-1591) established the foundation of Chanoyu (The Japanese style of tea ceremony) which has been said to offer a comprehensive model for life. Currently in Japan, green tea is regarded as a healthy beverage by the public. The term ‘green tea’ refers to the product manufactured from fresh tea leaves by careful steaming or roasting to avoid oxidation of the polyphenolic components known as catechins. The major catechins in green tea are (-)-epicatechin (EC), its hydroxyl derivative (-)-epigallocatechin (EGC), and their respective gallic acid esters, (-)-epicatechin-3-gallate (ECg) and (-)-epigallocatechin-3-gallate (EGCg) (Figure 1). Among green tea catechins, EGCg is abundant in green tea leaves, and has been shown to exhibit strong health-promoting activity [1,2], according to structure activity relationship assessment on EGCg, two close parallel aromatic rings and a third aromatic ring vertical to the two parallel rings may play a key role in the pharmacophore activity. This activity may be associated with the number of -OH groups in the catechin [3].

An understanding of the pharmacokinetic properties of green tea catechins is vital for promoting the human health benefits of its consumption. To assess the pharmacokinetics of green tea catechins after ingestion, we developed a new analytical method for detecting green tea catechins in serum. Pharmacokinetic study using this method showed individual variation of catechin serum concentration after ingestion of same amount of green tea catechins [4]. This observation indicated the existence of unknown factors affecting the pharmacokinetics of green tea catechins.

Numerous studies have shown that catechins have anti-cancer, hypotensive, and hypocholesterolemic activities [5-10]. Consistently, inverse relationships between green tea consumption and the reduction of cancer incidence, the risk of developing hypertension, and cholesterol level have also been demonstrated in epidemiological studies.

Previously, the in vitro anti-cancer effects of a green tea extract on Adult T-cell Leukemia (ATL), which is an endemic disease caused by a latent infection of human retrovirus HTLV-1, have been demonstrated [11]. Furthermore, to investigate an intervention study, the in vivo effects of drinking green tea on HTLV-1 provirus load in asymptomatic HTLV-1 carriers have been conducted [12]. By integrating the results of these studies, we proposed a possible mechanism of the anti-cancer effect of EGCg was proposed in this review.

Habitual green tea drinking has been shown to reduce other lifestyle-related diseases. We review experimental and epidemiological evidence to demonstrate that green tea consumption is good for human health.

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Received November 15, 2014; Accepted January 27, 2015; Published February 02, 2015

Citation: Sonoda J, Narumi K, Akio K, Erisa T, Toshiro M (2015) Green Tea Catechins -Pharmacokinetic Properties and Health Beneficial Effects. Pharm Anal Acta 6: 333. doi:10.4172/2153-2435.1000333

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General cancer: Fewer studies have reported the interaction between catechins and efflux transporters, possibly due to the instability of polyphenolic structures in cell culture medium or saline buffers caused by antioxidant level, pH of culture condition, concentration of proteins or the presence of metal ions [28]. To improve the stability of catechins in saline buffers, addition of a small amount of ascorbic acid (around 100 μM) as an antioxidant is recommended [22,24].

Anti-cancer effects of green tea drinking

Human studies

General cancer: Imai et al. showed an association between green
A case-controlled study conducted in Okinawa, in the south of Japan, showed that daily tea consumption significantly decreased the risk of lung cancer, especially for squamous cell carcinoma [43]. Contrarily, Li et al. demonstrated in a population-based cohort study in Miyagi, in northeastern Japan, that there was no association between green tea consumption and the risk of lung cancer [44]. To address these conflicting views, Wang et al. performed a meta-analysis of 38 lung cancer studies (26 case-controlled studies and 12 cohort studies) with 59,041 cases and 396,664 controls. The results showed that overall tea consumption was significantly associated with a decreased risk of lung cancer (RR, 0.78; 95% CI, 0.70–0.87) [45].

**Leukemia cancer:** Based on epidemiological evidence and our preliminary experimental study [11], authors attempted to apply green tea for Adult T-cell Leukemia (ATL). The causative agent of ATL is the human retrovirus, HTLV-1. HTLV-1-infected individuals are prevalent worldwide but clustered the endemic area including southwestern Japan. Therefore, we investigated green tea as a chemopreventive agent in ATL development. We conducted an intervention study to investigate the in vivo effect of green tea on HTLV-1 provirus load in peripheral blood lymphocytes (PBLs) of HTLV-1 carriers. The subjects enrolled in this study were asymptomatic HTLV-1 carriers. They were randomly assigned to two groups. GT (+): no intake of any green tea capsules (n = 46), and GT (+): received 9 green tea capsules per day (n = 37). Among the subgroup with a higher provirus load, a decreasing trend in HTLV-1 provirus load values was observed in the GT (+) group (regression coefficient (RC) = -0.072, SE=0.0430), but not in the GT(-) group (RC= +0.012, SE=0.043). A significant difference in HTLV-1 provirus load from baseline to each follow-up month between the GT (-) and GT (+) groups was observed at the 5 month [12].
Summary for human studies: Green tea consumption may preferentially offer some protection against hormone-associated cancer cells, including prostate and breast cancer cells [46]. Although green tea catechins, especially EGCG, strongly inhibit cellular proliferation or cell viability in other cancer cell lines, including oral, esophageal, bladder and skin cells, less information from cohort, case-controlled, or interventional studies on humans has been performed [5]. Recently, Hou et al. reviewed 17 epidemiological studies for stomach cancer, and found that all studies that analyzed men and women separately suggested a reduced risk in women compared to men, albeit the difference was not significant [47]. The inconsistent results between the epidemiologic studies may be due to variables such as differences in tea preparation and consumption, the methods of tea production, the bioavailability of tea compounds, and genetic variation in how the human body responds to tea consumption.

Proposed Mechanism of the Anti-cancer Effects
(Experimental Studies)

We have shown that EGCG markedly inhibits cell proliferation. Furthermore, under identical conditions, EGCG suppressed Bcl-xL mRNA expression in non-small-cell lung cancer A549 cells [48]. Bcl-xL, a member of the Bcl-2 family, inhibits apoptosis by blocking the mitochondrial cytochrome c release [49, 50]. A decrease in Bcl-xL gene expression may lead to the promotion of cell death. We predict that NF-κB inactivation by catechins, which is an upper stream event, may be essential for the induction of apoptosis. Several cell culture studies have focused on one of the hallmarks of apoptosis induction by green tea catechins, namely NF-κB [51, 52]. NF-κB is a nuclear transcription factor that regulates expression of genes that are critical of the regulation of apoptosis. NF-κB is bound in a complex in cytosol with inhibitor IκB. When IκB is degraded by proteasomes, NF-κB enters the nucleus and transcript target genes such as apoptosis-inhibiting genes. The suppression of NF-κB activation may lead to induce apoptosis. Gupta et al. revealed that EGCG reversed the degradation of IκBα, inhibitor protein of NF-κB, in a cytoplasmic extract. Subsequently, NF-κB activation is down-regulated and apoptosis is induced in A431 human epidermoid carcinoma cells [53]. On the other hand, the vascular endothelial growth factor (VEGF) is the most critical regulator in development of solid tumors. Indeed, human monoclonal antibody against VEGF, Bevacizumab, is utilized as the molecular target in clinical use. Recently, Gu et al. reported that EGCG suppresses breast tumor growth by inhibiting the activation of NF-κB and VEGF expression. Oral administration of EGCG significantly reduced tumor VEGF expression in a mouse breast cancer model, in which mammary glands were inoculated with breast cancer cells. It was also shown that EGCG significantly inhibited the activation of NF-κB in cultured cells [54]. Integrating these evidences, we hypothesized possible mechanism of apoptotic cell death and VEGF suppression by EGCG. That is, EGCG stabilize IκB and abrogates NF-κB activation. Then, suppression of the apoptosis-inhibiting protein Bcl-xL causes the release of cytochrome c from mitochondria. The activation of caspase signaling induces apoptosis, which is accompanied by a concomitant reduction in VEGF expression might lead to the suppression of angiogenesis (Figure 3).

Green Tea Effect on Lifestyle-related diseases

Recently, Kokubo et al. reported on the impact of green tea consumption on the incidence of cardiovascular disease and stroke in the Japanese population [55]. In this study, high green tea consumption was found to be inversely associated with the incidence of cardiovascular disease, stroke and stroke subtypes. The result verified by the Japan Public Health Center-Based Study Cohort was consistent with distinct study of The Tokamachi-Nakasato study cohort study in Japan [56].

Hypertension is one of the major risk factors of cardiovascular disease or stroke. Yang et al. reported that habitual tea consumption of 120 mL/d or more for 1 year significantly reduced the risk of developing hypertension in the Chinese population. This demonstrates the negative correlation between the amount and duration of tea consumption on the systolic and diastolic blood pressures. Multiple logistic regression models of the effect of the amount and duration of tea consumption on hypertension have been generated. Compared with non-habitual tea drinkers, the risk of developing hypertension was decreased by 45% for those who drank 120 to 599 mL/d, and was further reduced by 65% for those who drank 600 mL/d [6]. One possible mechanism of the effect of green tea on hypertension is the activation of the Akt and endothelial NO synthase (eNOS) pathways. Akt is a serine/threonine protein kinase that is activated by a phosphatidylinositol-3 kinase, which regulates phosphorylation eNOS. eNOS is involved in NO release and vasorelaxation. Ihm et al. assessed the level of phosphorylated Akt and eNOS in aortic rings in a rat model of metabolic syndrome (MS). Although MS rats showed low levels of phosphorylated eNOS and Akt, treatment with a green tea extract (namely, oral administration of 25 mg/kg/d for 12 weeks) increased eNOS and Akt phosphorylation [7].

The effect of green tea administration on serum cholesterol levels is shown. Wu et al. conducted a 2-month controlled green tea intervention study. Postmenopausal women were randomized into three arms: placebo, 400 mg of EGCG as a green tea extract capsule (PPE), or 800 mg of EGCG as a PPE. Total cholesterol and LDL-cholesterol decreased significantly in both PPE groups. The LDL-cholesterol level differed significantly between the placebo and PPE groups [8]. While the mechanisms by which green tea influences LDL-cholesterol levels remain unknown, animal studies showed that green tea extracts inhibit intestinal absorption of lipids and up regulate lower-density lipoprotein receptors in livermain lead to increase the efflux of cholesterol from liver cells [57].

Most recently, the effect of green tea on blood pressure and lipid profile was assessed by meta-analysis of randomized clinical trial. Based on the results of meta-analysis which included 20 RCTs and 1536 participants, green tea intake results in significant reductions in systolic blood pressure, total cholesterol, and LDL-cholesterol. The

![Figure 3: The possible mechanism of apoptotic cell death and anti-angiogenesis by EGCG.](image-url)
effects appear greater with longer duration of intervention [58].

Conclusion
Since green tea catechins absorption after one regular cup of green tea intake is relatively low (estimated in 10s to 100s μM range), it is difficult to obtain a similar result of anti-cancer effects observed in in vitro cell culture study (in 10s to 100s μM range). However, epidemiological studies shown in this review suggesting that larger portion of green tea consumption for a long term might reduce not only the risk of cancer, but also other lifestyle-related disease incidence. We concluded habitual green tea drinking is good for health.

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