Pharmacological Research 62 (2010) 457–464

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Tea catechins as inhibitors of receptor tyrosine kinases: Mechanistic insights and human relevance

Christine A. Larsen[a], Roderick H. Dashwood[a,b,*], William H. Bisson[c]

[a] Linus Pauling Institute, Oregon State University, Corvallis, OR, USA
[b] Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis, OR, USA
[c] Pharmaceutical Biochemistry Group, School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 22 July 2010
Received in revised form 27 July 2010
Accepted 28 July 2010

Keywords:
Receptor tyrosine kinases
Green tea polyphenols
Hepatocyte growth factor
Met signaling

ABSTRACT

Receptor tyrosine kinases (RTKs) play important roles in the control of fundamental cellular processes, influencing the balance between cell proliferation and death. RTKs have emerged as molecular targets for the treatment of various cancers. Green tea and its polyphenolic compounds, the catechins, exhibit chemopreventive and chemotherapeutic properties in many human cancer cell types, as well as in various carcinogenicity models *in vivo*. Epidemiological studies are somewhat less convincing, but some positive correlations have been observed. The tea catechins, including (−)-epigallocatechin-3-gallate (EGCG), have pleiotropic effects on cellular proteins and signaling pathways. This review focuses on the ability of the tea constituents to suppress RTK signaling, and summarizes the mechanisms by which EGCG and other catechins might exert their protective effects towards dysregulated RTKs in cancer cells. The findings are discussed in the context of ongoing clinical trials with RTK inhibitors, and the possibility for drug/nutrient interactions enhancing therapeutic efficacy.

Contents

1. Introduction

The cultivation of the tea plant dates back to more than 5000 years, and originally its leaves were used medicinally. Today it is a popular beverage that is consumed by two-thirds of the world's population. In recent years, green tea has received attention for its beneficial health effects, in particular the prevention of cancer. In 2009, Yang et al. reviewed the possible targets that could account for the chemopreventive effects of (−)-epigallocatechin-3-gallate (EGCG) [1]. The diverse mechanisms included inhibition of matrix metalloproteinases, cyclin dependant kinases, proteosomes, DNA methyltransferase, vitmentin, BCL-2, mitogen-activated protein kinase (MAPK) and receptor tyrosine kinase (RTK) pathways.

This review focuses specifically on the effects of tea and its constituents towards RTKs. First, the biochemical properties and bioavailability of the tea catechins will be discussed. Then, the abil-

* Corresponding author at: Weniger 503, Linus Pauling Institute, Oregon State University, Corvallis, OR 97331-6512, USA. Tel.: +1 541 7375086.
E-mail address: Rod.Dashwood@oregonstate.edu (R.H. Dashwood).

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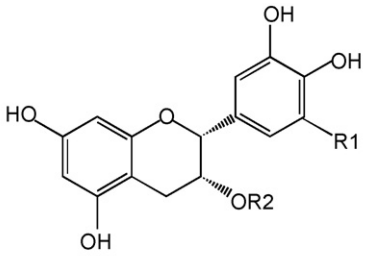
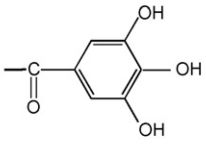
doi:10.1016/j.phrs.2010.07.010



Generic Tea Catechin Structure



Gallate group

Tea Catechin	Abbreviation	R1	R2
Epicatechin	EC	H	H
Epigallocatechin	EGC	OH	H
Epicatechin gallate	ECG	H	Gallate
Epigallocatechin gallate	EGCG	OH	Gallate

Fig. 1. Structure of tea catechins.

ity of tea to inhibit tumorigenesis in animal models and human epidemiological data will be presented. RTKs and their downstream signaling pathways will be described. Finally, the interaction of tea catechins with these pathways and potential mechanisms of action will be covered.

2. Tea and cancer chemoprevention

Aside from water, tea is the most widely consumed beverage worldwide [2]. This popular beverage has gained much attention for its purported health benefits, in particular for its possible role in preventing and treating cancer [3]. The chemistry of green tea, compared to other teas, is quite well characterized [4]. Green tea is produced by steaming or pan-frying the leaves of the *Camellia sinensis* plant. This process prevents the oxidation of the tea constituents. Among these constituents is a class of polyphenolic compounds known as the catechins (Fig. 1). Green tea catechins (GTCs) include (−)-epicatechin (EC), (−)-epigallocatechin (EGC), (−)-epicatechin gallate (ECG), and EGCG.

A typical cup of brewed green tea has been defined as 2 g of tea leaves in 200 mL of hot water. The catechins make up 30–40% by dry weight of the water extractable material [5]. EGCG is the best studied and most abundant of the tea catechins, accounting for 50–80% of the total catechin content. This represents 200–300 mg per cup of brewed green tea [6].

Catechin pharmacokinetics has been studied by several groups. Tea catechins undergo methylation, glucuronidation, sulfation and ring fission metabolism [7–9]. The biotransformation of tea catechins was reviewed by Lambert et al. [10]. In one study, rats and mice were given 0.6% GTCs as drinking fluid [11]. EGCG accounted for 78% of the catechins present, but plasma concentrations were much lower for EGCG than EGC and EC. High levels of EGCG were found in the feces whereas high levels of EGC and EC were found in urine. In another study, examination of tissues showed that EGCG was distributed widely in the colon, small intestine, liver, lung, and other organs [8]. After intravenous administration of green tea to rats, EC was found mainly in the intestine, bladder and kidney, EGC was found in the intestine, bladder, kidney and lung, and EGCG was found mostly in the colon and liver [11,12].

Table 1
Summary of animal data in which tea or tea compounds were used as chemopreventive agents.

Tea and inhibition of cancer in animal models		
	Positive results	Negative results
Lung	23 (2)	3
Bladder	3 (1)	0
Oral Cavity	6	0
Esophagus	5	0
Stomach	9	0
Small intestine	9	1
Colon	11 (3)	6
Liver	8 (1)	1
Pancreas	2 (2)	0
Prostrate	7 (5)	0
Breast	10 (10)	0
Thyroid	1	0
Skin	29 (2)	0

Updated from Ref. [1] with data current as of June 2010. The number of xenograft studies is shown in parentheses.

In humans, high concentrations of individual catechins were administered orally. The plasma concentration for each catechin was observed to be as high as 1.53 μM for a dose of 1050 mg EC [13], 3.1 μM for a dose of 644 mg ECG [14], 5 μM for a dose of 459 mg EGC [14], and 6.35 μM for a dose of 1600 mg EGCG [15]. Recently, it was reported that in patients with an ileostomy, 70% of flavonols (which includes catechins) from orally consumed green tea was found in the small intestine. Plasma and urine contained comparatively low levels, suggesting that after oral ingestion the catechins accumulate in the intestines [16].

Tea extracts and tea constituents have gained much attention for their abilities to inhibit tumor formation in different animal models (reviewed in Refs. [6,17–20]). The inhibition of small intestine, colon, prostate, bladder, breast, stomach, liver, pancreas, esophagus, oral cavity, lung and skin cancers has been reported in animal models (Table 1). Although mostly positive (i.e. chemopreventive) results were reported, some equivocal findings were noted in which tea had no apparent protective effects. Many variables could explain inconsistencies in these studies. Differences in diets used, protocol for tumor initiation, the type and dose of tea polyphenols or extracts used may explain the variability in some of the animal study results. Another key issue may be the stability of tea polyphenols in solution and in the diet.

A clear-cut association between human cancer risk and tea consumption may be more difficult to establish from epidemiological studies. There are many reviews on this topic [21–27]. Some studies show a negative association, others report no association, and a positive association has been observed in other investigations. Most recent reviews conclude that the protective effects of tea depend on the various etiological factors involved in different cancer types, and even for the same cancer types in different geographical areas. Furthermore, the consumption of green and black tea differs significantly among the various populations examined. Due to the large differences between epidemiological studies, it is perhaps naïve to expect a simple conclusion concerning tea and cancer prevention in human populations.

Case–control studies and cohort studies have observed an association between green tea consumption and lowered risk for stomach cancer in Japan (reviewed in Refs. [26–28]). One of the most promising intervention studies was performed by Bettuzzi et al. [29]. Two hundred individuals with high-grade prostate intraepithelial neoplasia received either 600 mg GTC or placebo for 12 months. In the GTC group only 3% developed prostate cancer, whereas 30% developed prostate cancer in the placebo group. The latter findings demonstrate the importance of carefully controlled