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Tea flavan-3-ols as modulating factors in endoplasmic reticulum function

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Abstract

Regular green tea consumption has been shown to reduce the risk of cancer and diabetes mellitus. These effects are attributed to tea flavan-3-ols, especially to epigallocatechin gallate; however, the molecular targets and mechanisms of action are still subject of extensive research. The special roles of the endoplasmic reticulum (ER) in biotransformation, protein synthesis, calcium homeostasis, and glucose production make this organelle a potential target of the antitumor and antidiabetic effects of tea flavan-3-ols. The purpose of this review is to present evidence for the biologic actions of tea flavan-3-ols on specific ER targets associated with normal function and disease. Reactivation of chemical carcinogens can be reduced by tea flavan-3-ols through inhibition of glucuronide transport across the ER membrane. Catechins modulate Ca^{2+} release from the ER lumen and interfere with glycoprotein maturation, which can lead to decreased viability and increased drug sensitivity of tumor cells. Epigallocatechin gallate inhibits glucose transport across the ER membrane, which can underlie the reduction of hepatic glucose production by tea flavan-3-ols. These mechanisms likely contribute to the chemopreventive and glucose-lowering effects of tea catechins. Investigating the effects of flavan-3-ols on ER functions is a promising field of medical and biochemical research to understand disease and improve health.

Keywords: Green tea; Polyphenols; Glucuronidation; Glycosylation; Glucose production

Abbreviations: ATPase, adenosine triphosphatase; BiP, immunoglobulin heavy chain binding protein; ECG, epicatechin gallate; EGCG, epigallocatechin gallate; ER, endoplasmic reticulum; ERAD, ER-associated degradation; G6P, glucose-6-phosphate; G6Pase, glucose-6-phosphatase; G6PT, G6P translocase; PLC, phospholipase C; RyR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum calcium ATPase; UGT, UDP-glucuronosyltransferase; UPR, unfolded protein response.

1. Introduction

Green tea, a beverage produced from the leaves of tea plant (*Camellia sinensis*), is one of the most widely consumed drinks in the world. It was already considered as a healthful beverage and remedy in the ancient Chinese medicine. The chemical constituents of tea received a great scientific interest in the past few years because of their beneficial health effects and the apparent lack of toxicity. Daily consumption of green tea was shown to decrease the risk of cardiovascular diseases, lower blood pressure, prevent the development of atherosclerosis, improve lipid profile, and have antithrombotic and anti-inflammatory properties. Tea also possesses antiviral and antibacterial activities, prevents dental caries, and promotes oral health. It has protective effects on neurons in neurodegenerative diseases, such as Alzheimer and Parkinson diseases, reduces the infarct volume in cerebral ischemic damage, and delays brain senescence [1].

Besides these important properties, the antitumor and antidiabetic effects of green tea should be emphasized.

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Bioactive compounds in tea have been reported to reduce blood glucose level, improve insulin sensitivity, influence adipocyte differentiation and proliferation, and decrease body weight and fat mass. Because of these favorable effects, green tea seems to be a potent agent in the prevention of diabetes mellitus. Nevertheless, the greatest attention was received by those observations, which highlighted that green tea consumption inhibits formation, growth, and invasion of malignant tumors. Green tea has significant genoprotective effects [2]: it increases the resistance of DNA to oxidative damage, inhibits malignant transformation and proliferation of cells, and has proapoptotic effect on transformed cells [3]. In addition, it suppresses angiogenesis [4] and the appearance of metastases [5]. Despite the high consumption of tobacco, Asian populations have remarkably low incidences of arteriosclerosis and lung cancer. This "Asian Paradox" is now most widely considered as a result of high consumption of green tea (often more than 1 L green tea every day) in this region [6].

Fresh leaves of the tea plant contain more than 700 chemicals, among which proteins, carbohydrates, lipids (linoleic acid), alkaloids (caffeine, theophylline, theobromine, xanthine), B vitamins (thiamine, riboflavin, pantothenic acid), vitamin C, minerals, and trace elements can be found. However, the most interesting constituents are the polyphenolic tea catechins (flavan-3-ols) because they are regarded as the biologically most active constituents of tea [7]. Polyphenols represent 30% of the dry matter in tea leaf; therefore, green tea can be considered as an important dietary source of catechins. Black or oolong tea is stained by dark polymerized compounds (eg, bisflavanols, theaflavins, epitheaflavic acids, and thearubigens), which are produced from monomeric catechins by the enzyme polyphenol oxidase during fermentation of tea leaves and impart the characteristic taste and color properties of black tea. Nonfermented green tea is produced by drying intact tea leaves to inactivate the oxidase enzyme before it could access its substrate catechins. Semifermented oolong tea is intermediate in composition between green and black teas [7,8].

Regarding their chemical structure, green tea polyphenols belong to the subgroup named *catechins*, also known as *flavan-3-ols*. Catechins possess 2 phenolic rings and a dihydropyran heterocycle. They vary with respect to the presence or absence of gallate and gallo moieties and to the configuration of the latter. Epigallocatechin gallate (EGCG), epigallocatechin, and epicatechin gallate (ECG), are the most abundant tea flavan-3-ols [9], among which EGCG is the most studied [10].

Flavan-3-ols, similarly to other polyphenols, are effective antioxidants, and this advantageous feature certainly contributes to the benefits of green tea consumption. However, as a result of extensive research in this field, a large number of alternative mechanisms of action have also been suggested for the dietary and pharmacologic effects of these compounds. Clarification of the precise mechanisms of action not only is an interesting academic question for scientists but also has a great impact on prevention and treatment of aforementioned diseases raising major medical problems nowadays, as well. Development of new therapeutic agents based on tea catechins is in progress, and nutritional supplements containing EGCG (eg, Teavigo capsule [11]) are available for people to enjoy its benefits without drinking several cups of green tea everyday.

The endoplasmic reticulum (ER) is a continuous membrane network in the cytosol of all eukaryotic cells. Its lumen forms a separate intracellular metabolic compartment involved in all branches of the intermediary metabolism [12], and several findings indicate the nutrient sensor function of the organelle [13,14]. The ER plays central roles in calcium homeostasis and protein processing. Dysfunction of the organelle, that is, the ER stress, causes accumulation of misfolded proteins in the lumen and leakage of Ca^{2+} to the cytosol. The activated signaling mechanisms largely affect the control of cell proliferation, differentiation, and death. The enzyme systems catalyzing major reactions of biotransformation and hydrolysis of glucose-6-phosphate are also localized in the ER. Therefore, the functions of this organelle are major determinants of active hormone levels, toxicity of chemical carcinogens, and glucose output from glucogenic tissues.

Several candidate molecular targets of tea flavan-3-ols are situated in the plasma membrane and in various compartments of the cell (eg, cytosol, mitochondria, nucleus) [15]. However, studies of the past few years revealed that modulation of enzyme or transport activities located in the ER might also significantly contribute to the beneficial antitumor and metabolic effects of tea flavan-3-ols. Alterations in deglucuronidation, protein processing and protein quality control, calcium homeostasis, or glucose production in the ER can contribute to prevention from chemical carcinogenesis, enhancement of tumor cell apoptosis, and reduction of hepatic glucose output. The aim of this review is to summarize the findings indicative of the significant role of the ER in health effects of tea flavan-3-ols (Table 1).

2. Deglucuronidation

A large number of endogenous and exogenous compounds, including chemical carcinogens [16], are inactivated and prepared for elimination in the ER lumen by conjugation with glucuronate (Fig. 1), a reaction catalyzed by UDP-glucuronosyltransferases (UGTs). Deglucuronidation is catalyzed by β-glucuronidases localized in the lysosomes, ER [17,18], and in intestinal bacteria [19]. Reactivation of chemical carcinogens by β-glucuronidase largely increases the risk of local malignant transformation [20-22]. Accordingly, the chemopreventive glucarate has been shown to hinder carcinogenesis in various tissues [23-27] through inhibiting β-glucuronidase. Glucuronides are polar compounds with charge at physiologic pH; thus, they cannot