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Review

# Protective role of epigallocatechin-3-gallate in health and disease: A perspective

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ABSTRACT

Tea is the most popular beverages all over the world. Polyphenols are found ubiquitously in tea leaves and their regular consumption has been associated with a reduced risk of a number of chronic diseases including cancer, cardiovascular and neurodegenerative diseases. Epigallocatechin-3-gallate (EGCG) is the most abundant polyphenol in tea leaves and received great attention due to their protective role in the prevention of the diseases. Rather than eliciting direct antioxidant effects, the mechanisms by which tea polyphenol express these beneficial properties appear to involve their interaction with cellular signaling pathways and related machinery that mediate cell function under both normal and pathological conditions. The central focus of this review is to provide an overview of the role that the major tea polyphenol, EGCG plays in preventing cancer, cardiovascular and neurodegenerative diseases. This review present epidemiological data, human intervention study findings, as well as animal and in vitro studies in support of these actions and delineates the molecular mechanism associated with the action of EGCG in ameliorating of such diseases.



**Contents**



## 1. Introduction

Tea is one of the most consumed beverages worldwide. At present, it is cultivated in at least 30 countries around the world. Tea produced from the leaves of the plant *Camellia sinensis*, a member of Theaceae family. In different parts of the world freshly harvested tea leaf is processed differently to give oolong tea (2%), green tea (20%) or black tea (78%) [1]. Green tea is prepared from the fresh tea leaf and widely consumed in Japan and China. Western cultures like to drink black tea which is prepared through the oxidation, curing process of maceration and exposure to atmospheric oxygen [2,3]. However, the health beneficial effect of green tea for a wide variety of diseases including different types of cancer, cardiovascular and lung diseases were extensively

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reported. The health benefits of consuming green tea and its constituents in ameliorating cancer and cardiovascular diseases are now well established [4–6]. Anti-inflammatory [7], antiarthritic [8], antibacterial [9], antiangiogenic [10], antioxidative [11], antiviral [12], neuroprotective [13], and cholesterol-lowering effects [14] of green tea and isolated green tea constituents provided hopeful results.

The health-beneficial effects of green tea are mainly attributed to its polyphenol content, particularly flavanols and flavonols, which represent 30% of fresh leaf dry weight [1,15,16]. The major flavonoids of green tea are various catechins [17]. There are four types of catechins mainly detected in green tea: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG) [18]. EGCG is renowned as the major catechin of green tea for its maximum health beneficial effect [19]. Several epidemiological studies show that green tea catechins provide some protection against degenerative diseases [20]. Some studies specified that green tea catechins have an antiproliferative activity and hypolipidemic activity in the prevention of hepatotoxicity [20] and also act as a preventive agent against mammary cancer post-initiation [20]. Green tea catechins were also found to be effective in inhibiting oxidative stress and consequently cardiovascular and neurological disorders [21,22]. In addition, green tea catechins could also act as antitumorigenic agents and as immune modulators in immunodysfunction caused by transplanted tumors or by carcinogen treatment [23]. This review elucidates the protective role of EGCG in human health and disease.

### 1.1. Chemical composition of tea

The green tea leaves contain carbohydrates (5–7% dry weight) such as cellulose, glucose, sucrose, fructose, pectins; proteins (15–20% dry weight), whose enzymes constitute an important fraction; amino acids (1–4% dry weight) such as serine, glutamic acid, tryptophan, tyrosine, valine, arginine, glycine, aspartic acid, leucine, threonine, and lysine; trace amounts of lipids (linoleic and α-linolenic acids), sterols (stigmasterol); minerals and trace elements (5% dry weight) such as calcium, magnesium, manganese, iron, chromium, zinc, copper, molybdenum, phosphorus, sodium, cobalt, selenium, strontium, potassium, nickel, and aluminum; vitamins such as Vit-B, Vit-C, Vit-E; pigments (chlorophyll, carotenoids); and volatile compounds (aldehydes, alcohols, esters, lactones, hydrocarbons). Fresh tea leaves contain, 3–4% of alkaloids known as methylxanthines, such as caffeine, theobromine, and theophylline and also phenolic acids for example, gallic acids [2].

Green tea also contains polyphenols, which include flavanols, flavandiols, flavonoids, and phenolic acids; these compounds may account for about 30% of the dry weight. Most of the green tea polyphenols (GTPs) are flavonols, commonly known as catechins. There are four types of catechins mainly detected in green tea: epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epigallocatechin-3-gallate (EGCG). The preparation methods influence the catechins both quantitatively and qualitatively. The amount of catechins differs in the original tea leaves because of differences in variety, origin and growing conditions [24]. The preparation of fresh green tea cannot extract the total catechins from the leaves; therefore, the concentration differs from the absolute values determined through the complete extraction of leaves [25]. However, catechins are relatively unstable and could be modified quantitatively during the time frame of an experiment [26,27]. As a result, comparison of ingested doses in animal studies seems difficult because the catechin quantification before administration is often not known. In the recent years, many of the health beneficial effects of green tea were credited to its most abundant catechin, EGCG [28,29].

### 1.2. EGCG on obesity and diabetes

The effects of tea on obesity and diabetes have received a great attention, especially EGCG, appear to have anti-obesity effects [30]. As the frequency of type 2 diabetes mellitus is increasing at a frightening rate, necessity of effective nutritional approaches for the prevention of this disease is very important. Specific dietary components having anti-diabetic efficacy could be one aspect of these strategies. Black tea extract has been shown to suppress the increase of blood glucose during food intake and reduce the body weight in diabetic mice [31]. However, epidemiological and clinical studies on the health benefits of EGCG on obesity and diabetes concerning the mechanisms of its actions based on various laboratory data are limited. Recent data from human studies showed that the consumption of green tea and green tea polyphenols may help in reducing body weight, mainly body fat by the increase of postprandial thermogenesis and fat oxidation [32]. Although a double-blind, placebo-controlled, cross-over design study showed that consumption of a beverage containing green tea catechins, caffeine and calcium increases 24-h energy expenditure by 4.6%, but the contribution of the individual components could not be differentiated. However, a study in the recent past reported that the body weights of rats and their plasma triglyceride, cholesterol and low-density lipoprotein cholesterol were significantly reduced by feedings of oolong black and green tea leaves to the animals, where EGCG plays the predominant role [32]. Another study indicated that mice fed with EGCG have been shown to decrease diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation [33]. In a randomized, double-blind, placebo-controlled and cross-over pilot study, six overweight men were given 300 mg EGCG daily for two weeks and their fasting and postprandial changes in energy expenditure and substrate oxidation were determined. The results indicated that resting energy expenditure did not differ significantly between EGCG and placebo treatments, interestingly during the first postprandial monitoring phase, respiratory quotient values were significantly lower with EGCG treatment compared to the placebo. These novel findings suggest that EGCG alone has the potency to increase fat oxidation and thereby shows anti-obesity effect. However, more successful studies with a greater sample size and a broader range of age and body mass index are needed to define the optimal dose.

Wolfram et al. [34] investigated the anti-diabetic effects of EGCG in rodent models of type 2 diabetes mellitus and H4IIE rat hepatoma cells. The study showed that EGCG beneficially modifies glucose and lipid metabolism in H4IIE cells and significantly enhances glucose tolerance. A recent study suggested that EGCG ameliorates glucose tolerance, increases glucose-stimulated insulin secretion and reduces the number of pathologically changed islets of langerhans, increases the number and the size of islets, and heightens pancreatic endocrine area in db/db mice. The mechanism of action of EGCG has been suggested due to having anti oxidative property [35]. A laboratory study investigated the effects of EGCG (25, 50, 100 mg/kg for 50 days) in rats with streptozotocin-induced diabetes and subtotal nephrectomy. EGCG reduced hyperglycemia, proteinuria, lipid peroxidation and also decreases advanced glycation end-product accumulation in the kidney cortex [36]. Waltner-Law et al. [37] provided in vitro evidence that EGCG decreases glucose production of H4IIE rat hepatoma cells. They demonstrated that EGCG induces an increase in tyrosine phosphorylation of the insulin receptor thereby mimicking insulin and also the insulin receptor substrate and reduces gene expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase. EGCG has also been shown to modulate glucose metabolism beneficially in experimental models of type II diabetes mellitus [38,39]. Furthermore, a previous study demonstrated that EGCG