Biomedicine & Pharmacotherapy 78 (2016) 50–59

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

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

Animesh Chowdhury, Jaganmay Sarkar, Tapati Chakraborti, Pijush Kanti Pramanik, Sajal Chakraborti*

Department of Biochemistry and Biophysics, University of Kalyani, Kalyani, 741235 West Bengal, India

ARTICLE INFO

Article history:
Received 4 October 2015
Received in revised form 3 December 2015
Accepted 15 December 2015

Keywords:
EGCG
Cancer
Cardiovascular diseases
Diabetes
Neurodegenerative diseases

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.

© 2015 Elsevier Masson SAS. All rights reserved.

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

* Corresponding author.
E-mail address: sajal_chakraborti@yahoo.com (S. Chakraborti).

http://dx.doi.org/10.1016/j.biopha.2015.12.013
0753-3322/© 2015 Elsevier Masson SAS. All rights reserved.

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

ameliorates cytokine induced b cell damage in vitro [40] and prevents multiple low doses of streptozotocin induced decrease of islet mass in vivo [41]. Lambert et al [42]. showed that intragastric administration of EGCG at a dose of 75 mg/kg resulted in a C_{max} of 128 mg/l total plasma EGCG and a terminal half-life of 83 min. Additionally, an oral intake of EGCG at a dose of 50 mg (0.7 mg/kg) resulted in a C_{max} of 130 mg/l total plasma EGCG and a terminal half-life of 112 min in humans [43].

Several research studies demonstrated that EGCG prevents adipocyte proliferation and differentiation [44–46], increases cellular defence against oxidative stress and blocks sodium-dependent glucose transporter 1 (SGLT1) and lipid micelle formation in the intestine [47,48]. Blockage of SGLT1 and lipid micelle formation is the most important mechanisms for EGCG to exert its effect against obesity and diabetes. However, there is a limitation to use these catechins as a remedy for these two metabolic diseases. Retinol-binding protein 4 (RBP-4) has recently been described as an adipokine that contributes to insulin resistance in the AG4KO mouse model [49]. It is mainly secreted by adipocytes, and act as a signal to other cells, when there is a decrease in plasma glucose concentration [50]. A recent study indicated that EGCG treatment to adipocytes up regulates RBP-4. The increased expression of RBP-4 after EGCG treatment was further recovered by co-treatment of methyl pyruvate with vitamin E, which is a cellular energy source by passing sodium-independent glucose transporters (GLUTs) and glycolysis, suggesting that impaired glucose uptake by EGCG appeared to be a causative mechanism for RBP-4 upregulation [51]. Thus, dietary supplementation with EGCG could potentially contribute to nutritional strategies for the prevention and treatment of type 2 diabetes mellitus.

1.3. EGCG and cancer

One third of the human cancers are caused by dietary lifestyle and moderate diet is the potential approach against this life threatening disease. Chemoprevention has become known as a practical strategy to reduce cancer incidence and as a result of the mortality and morbidity associated with this severe disease. A perfect chemo preventive agent for humans should have high efficacy in multiple sites, a known mechanism of action and minimal side effects. Additionally, it should be nontoxic to normal cells, easy to oral consumption, cost-effective, suitably bio-available and with human acceptance. The use of tea, as a cancer chemo preventive agent gained worldwide appreciation in the last twenty five years. Epidemiological as well as laboratory studies have indicated tea consumption conversely associated with the progression of certain cancer types [52–54]. It has now been suggested that tea polyphenols potently induce apoptotic cell death and cell cycle arrest through several biological pathways in tumor cells, but not in their normal cells [55]. According to results from several epidemiological studies, individuals who drink green tea regularly may have less frequent or less severe cancer in various areas of the body such as in the ovary and prostate [56–58]. There are many evidences which suggest that regular intake of green tea at a level of more than three cups daily may reduce the chance of lung cancer in smokers [59]. The inhibitory effects of tea polyphenols on tumorigenesis in the digestive tract, including the oral cavity, esophagus, stomach, small intestine, and colon, have also been found in more several studies [60–63]. Additionally, there are a large number of studies concerning the relation between tea polyphenols and colorectal cancer [64]. Consumption of tea catechin capsules after one year inhibited the conversion of high-grade prostate intraepithelial neoplasia to cancer in comparison to a placebo [65].

When tea preparations were administered during the initiation, promotion, or progression stages of carcinogenesis in rats, the inhibitory activity of the main tea catechin, EGCG has also been studied in the laboratory. Laboratory studies suggested that EGCG works mainly at the cellular level to intervene against various cancers, including breast [66,67]; pancreas [68]; mouth [69]; colon [70] and prostate [71,72]. Khan and Mukhtar [73] described the pathways involved in cancer chemoprevention by EGCG as causing inhibition of: (1) mitogen-activated protein (MAP) kinases and activator protein-1 (AP-1), (2) nuclear factor-κB (NF-κB) signaling pathway, (3) epidermal growth factor receptor (EGFR)-mediated pathways, (4) insulin-like growth factor (IGF)-1 mediated signal transduction pathways, (5) proteosome activities, (6) MMPs activity, (7) urokinase-plasminogen activator activities and (8) induction of apoptosis and cell cycle arrest.

Yamamoto et al. [74] reported that EGCG could be used to enhance the effectiveness of chemo/radiation therapy to induce cancer cell death while protecting the normal cells. EGCG consumption by green tea has been shown to prevent breast cancer [75,76]. A recent study suggested that combination therapy of curcumin and EGCG function as antitumor agents for suppressing breast cancer stem cells (BCSCs) through regulating STAT3 and NFκB signaling pathways, which could serve as targets for reducing the CSCs leading to novel targeted-therapy for treating breast cancer [77]. EGCG has also been shown to potentiate the effect of curcumin in inducing growth inhibition and apoptosis of resistant breast cancer cells [78]. Another recent study indicated that, EGCG prevents cell growth and proliferation of MCF-7 breast cancer cells, possibly by inhibiting the protein expression of HIF-1α and VEGF [79]. A previous finding indicated that EGCG suppresses the growth, migration and invasion of human triple negative breast cancer cells by inhibiting VEGF expression [80].

Tamoxifen elicits proapoptotic effects in ER-negative breast cancer through the modulation of cell signaling pathways in an ER-independent manner. However, these effects have been mostly reported with high concentrations of tamoxifen. The combination of tamoxifen with green tea catechins could enhance its action in ER-negative breast cancer. In addition, such a combination could allow a dosage reduction of breast endocrine treatment in ER-positive breast cancer and in breast cancer chemoprophylaxis leading to an amelioration of the safety profile [81]. In this regard, Huang et al. [82] showed that a co-treatment with 5 μM EGCG and 200 nM tamoxifen had a synergistic effect in the inhibition of MCF-7 and AU565 breast cancer cell growth through the down-regulation of the Skp2 protein, an S-phase kinase protein 2 (Skp2), component of the Skp1-cullin 1-Fbox protein (SCF) ubiquitin ligase complex, which modulates the p27 proteolysis, a key regulator of G1-to-S phase progression. Zhou et al. [83] also reported that breast cancer is significantly less prevalent among Asian women, who consume high intake of EGCG as dietary intervention.

EGCG has been shown to inhibit the growth of human lung cancer cells in test tubes [84]. A previous experimental report indicated the anticarcinogenic activity of EGCG to inhibit lung cancer [85]. Combination therapy of Leptomycin B (LMB) and EGCG augments LMB-induced cytotoxicity through enhanced ROS production and the modulation of drug metabolism and p21/survivin pathways and prevents the development of lung cancer and act as a promising anti-lung cancer drug [86]. A recent research postulated that EGCG inhibits nicotine-induced migration and invasion by the suppression of angiogenesis and epithelial-mesenchymal transition (EMT) and prevents lung cancer progression [87]. The inhibition of cell proliferation of human non-small-cell lung cancer A549 cells by EGCG achieved via suppressing the expression of the cell death-inhibiting gene, Bcl-xL [88]. A recent data suggested that EGCG impedes proliferation of lung cancer cells including their chemo-resistant variants through down

regulation of Axl and Tyro 3 expression [89]. Furthermore, EGCG has been reported to strongly suppress lung tumorigenesis through its binding with Ras-GTPase-activating protein SH3 domain-binding protein 1 (G3BP1) [90]. Ma et al. [91]reported the anti-lung cancer activity of EGCG through the inhibition of the EGFR signaling pathway. Anti-proliferative effects of EGCG on A549 lung cancer tumor growth and angiogenesis has also been reported [92]. A recent intensive study suggest that EGCG could have an effective inhibitory effects on tumor angiogenesis induced by insulin-like growth factor-I (IGF-I) in human lung cancer cells, which may occur through the down regulation of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) expression [93]. EGCG has also been shown to inhibit MDM2-mediated p53 ubiquitination that may partly contribute to the anti-lung cancer activity of EGCG [94]. Ko et al. [95] recently demonstrated that EGCG inhibits transforming growth factor-β1 (TGF-β1)-mediated EMT by suppressing the acetylation of Smad2 and Smad3 and impedes lung tumorigenesis. Deng and Lin [96] recently suggested that EGCG inhibits the invasion of highly invasive CL1-5 lung cancer cells by suppressing MMP-2 expression via JNK signaling pathway and impedes lung cancer inducing G2/M arrest.

In relation to prostate cancer, Gupta et al. [97] and Adhami et al. [98] reported that tea polyphenols, mainly EGCG could inhibit the development of prostate cancer in an animal experiment. Paschka et al. [99] suggested that EGCG is the most effective catechin in inhibiting prostate cancer cell growth via apoptotic cell death as shown by changes in nuclear morphology and DNA fragmentation. On the other hand, Brusselmans et al. [100] demonstrated that EGCG prevents prostate cancer cell growth by inducing apoptosis through the inhibition of fatty acid synthase (FAS) activity and could be used as a potent chemopreventive and therapeutic antineoplastic agent for prostate cancer.

A dose of 15 μmole EGCG/mouse for 7 days prior to initiation with 7,12-dimethylbenz(a) anthracene (DMBA) followed by twice weekly treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA) as the tumor promoter resulted in significant prevention against skin tumor initiation in SENCAR mouse skin [101]. In these experiments, pretreatment of EGCG to the SENCAR mouse to that of carcinogen treatment was found to cause 30% inhibition in carcinogen metabolite binding to epidermal DNA suggesting EGCG may have the capability of inhibition of the metabolism of the precarcinogen [101]. Fig. 1 schematically represents the possible role of EGCG in prevention of cancer.

1.4. EGCG and cardiovascular diseases

Cardiovascular disease (CVD) includes all the diseases of the heart and associated blood vessels including coronary heart disease, heart failure, cardiomyopathy, and rheumatic heart

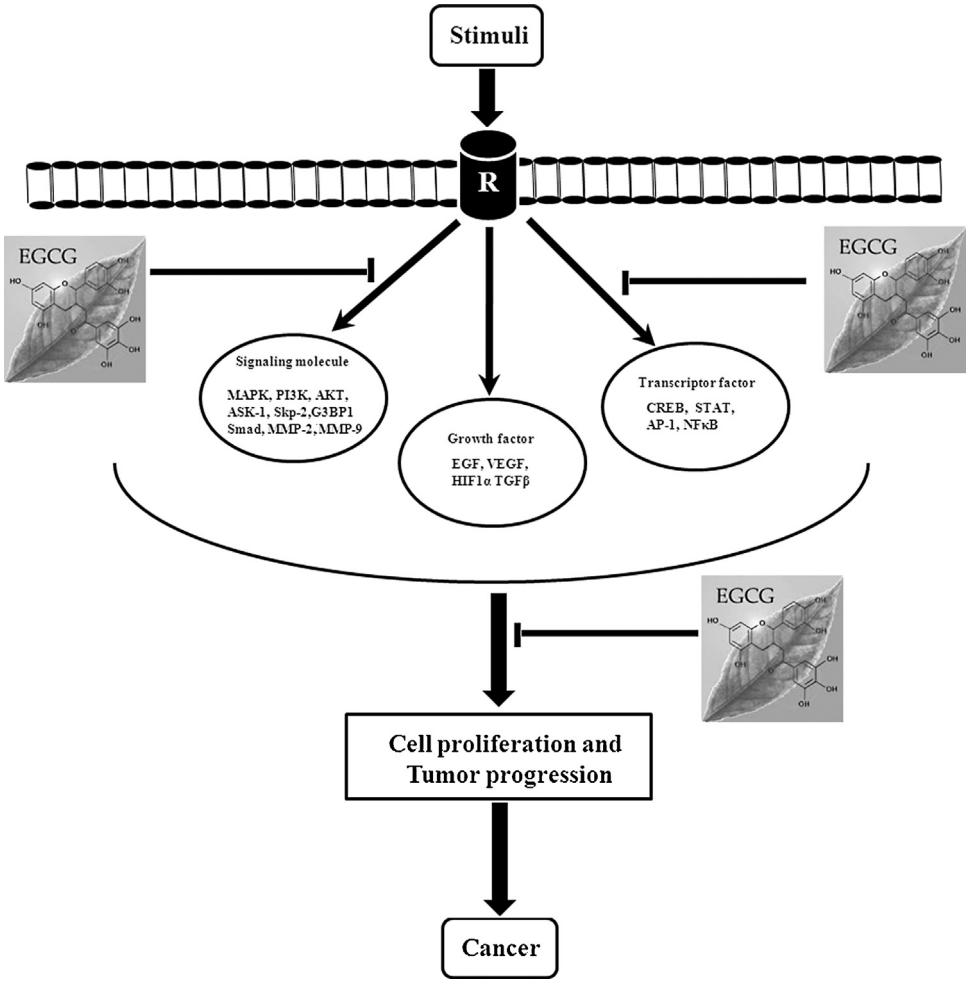

Fig. 1. Role of EGCG in inhibiting cancer. R: receptor; MAPK: mitogen activated protein kinase; PI3K: phosphoinositide 3-kinase; ASK-1: apoptosis signal-regulating kinase 1; Skp-2: S-phase kinase-associated protein 2; G3BP1: Ras GTPase-activating protein-binding protein 1; MMP-2: matrix metalloproteinase-2; MMP-9: matrix metalloproteinase-9; EGF: epidermal growth factor; VEGF: vascular endothelial growth factor; HIF1α: hypoxia-inducible factor1 α; TGFβ: transforming growth factor β; CREB: cAMP response element-binding protein; STAT: signal transducer and activator of transcription; AP-1: activator protein 1; NF-κB: nuclear factor κB.

disease. CVD is one of the major causes of morbidity and mortality worldwide. One of the prevalent of CVD is atherosclerosis. This occurs due to an abnormal build-up of plaque formation of fat and other substances inside the arteries. Atherosclerosis is most serious in the condition when it reduces blood supply to the heart (causing angina or heart attack). A range of genetic and environmental factors play a key role in initiation, progression and development of CVDs; however, it is difficult to explore the impact that an individual factor, for example, a specific dietary nutrient on the progression of CVD. However, regular consumption of polyphenol-rich beverage tea may exert cardio-protective effects in humans. Furthermore, meta-analyses have indicated that the consumption of three cups of tea per day reduces CVD risk by 11% [102].

Several epidemiological studies indicated that tea consumption is one of the factors to affect the risk of CVDs and it could uniformly lower the rate of heart diseases [103]. The first study indicating a protective effect of tea on atherosclerosis in experimental animals was published in 1967 [104] suggesting consumption of tea seemed to reduce the extent of atherosclerosis in hypercholesterolemic rabbits. A previous report suggested that green tea polyphenols consumption for 4 months significantly reduced aortic atherosclerosis in hypercholesterolemic rabbits [105]. Likewise, green tea intake reduced atherosclerotic plaque formation by 30% in rabbits fed a high-fat diet supplemented with 0.15% cholesterol [106]. Additionally, the effectiveness of EGCG against rabbit atherosclerosis was significantly improved by incorporating EGCG into the nanoformulation [107]. EGCG has been shown to ameliorate *Porphyromonas gingivalis*-induced atherosclerosis in mice model [108]. Ramesh et al. [109] suggested that EGCG improves serum lipid profile and erythrocyte and cardiac tissue antioxidant parameters in Wistar rats fed an atherogenic diet. Ramesh et al. [110] also suggested the inhibitory effect of EGCG on the expression of C-reactive protein and other inflammatory markers in an experimental model of atherosclerosis and may have potency to decrease CVD. In another study, the effects of EGCG on atherosclerotic plaque development were investigated in apolipoprotein E-null mice [111]. Intraperitoneal administration of EGCG (10 mg/kg for 42 days) reduced atherosclerotic lesions formation by 73% after cuff-injury of the carotid artery [112].

The cardiovascular benefit of EGCG was also observed in a study with isolated guinea pig hearts in which EGCG added to the perfusion medium (10 and 100 μM) increased left ventricular pressure, as well as nitric oxide and calcium content of the heart without increasing the heart rate exhibiting the positive inotrophic effects without accompanying positive chronotrophic effects in an NO-dependent manner [113]. The effect of EGCG on myocardial ischemia-reperfusion injury was investigated in rats [114]. EGCG was administered intravenously (10 mg/kg) at the end of the 30-min ischemia period, followed by continuous infusion during the reperfusion period (10 mg/kg/h). EGCG administration significantly reduced myocardial injury (myocardial damage score and plasma creatine phosphokinase), plasma interleukin-6 and neutrophil infiltration [114]. Li et al. [115] investigated the effects of EGCG on cardiac hypertrophy in vitro and in vivo induced by pressure overload due to constriction of the abdominal aorta in rat model. EGCG treatment (50 mg/kg orally for 21 days) has been shown to prevent the overload-induced cardiac hypertrophy.

In other ways, EGCG in combination with zinc has been reported to protect cardiac myocytes against hypoxia/reoxygenation (H/R)-induced apoptotic cell death and suggested as the effective agents for use in the prevention of ischemia-reperfusion (I/R) injury in clinical practice and subsequenty ameliorate coronary artery disease (CAD) [116]. Widlansky et al. [117] indicated that EGCG infusion acutely improves endothelial dysfunction in humans and reduces the possibility of CAD. EGCG has also been shown to inhibit STAT-1 activation and protects cardiac myocytes from I/R-induced apoptosis and act as a cardio protective agent in CAD. Fig. 2 schematically represents the role of EGCG in prevention of cardiovascular diseases.

1.5. EGCG and cerebral ischemic stroke

An intensive study demonstrated that intra-cerebroventricular injection of EGCG immediately following ischemia, inhibits endoplasmic reticulum stress (ERS) and improves the neurological status of rat model of stroke that have undergone middle cerebral artery occlusion via the inhibition of calpain-mediated proteolysis of the transient receptor potential cation channel, TRPC6 and the subsequent activation of cAMP response element-binding protein (CREB) via the MEK/extracellular signal-regulated kinases (ERK) pathway [118].

EGCG has also been shown to improve the efficiency of synaptic transmission in cerebral ischemia injury with attenuated effect related to the neuroprotection of EGCG by regulating excitatory and inhibitory amino acid balance [119]. Lim et al. [120] evaluated the functional effect of EGCG on ischemic stroke in rat model and suggested that EGCG may induce functional improvement of forelimb in middle cerebral artery occlusion (MCAO) rat model with ischemic stroke during the acute or subacute period. A recent study investigated the effect of EGCG on memory and learning after ischemia and demonstrated a functional improvement in a transient middle cerebral artery occluded rat [121]. Suzuki et al. [122] investigated the protective effects of green tea catechins on cerebral ischemic damage and suggested that daily intake of green tea catechins, mainly EGCG efficiently protects the damage caused by cerebral ischemia. Uchida et al. [123]indicated that EGCG may prevent incidence of stroke due to the radical scavenging action and inhibition of lipid peroxidation and may result in prolonging the life span of stroke-prone spontaneously hypertensive rat (SHRSP).

1.6. EGCG and lung diseases

Lung diseases are one of the most common in the world. Relatively small number of studies has been performed with the effect of the tea polyphenolic component catechins on lung diseases and the role that EGCG plays in this regard is limited.

Investigation with the effect of EGCG on lung injury, Giakoustidis et al. [124] performed a study examining the effect

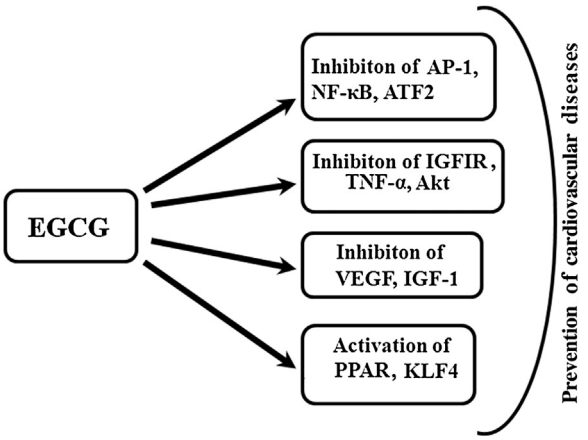

Fig. 2. Role of EGCG in preventing cardiovascular diseases. AP-1: activator protein 1; NF-κB: nuclear factor κB; ATF2: activating transcription factor 2; TNFα: tumor necrosis factor α; VEGF: vascular endothelial growth factor; IGF-1: Insulin-like growth factor; PPAR: peroxisome proliferator-activated receptor; KLF4: kruppel-like factor 4.

of EGCG on I/R induced lung injury. In this study, thirty number of male Wistar rats were divided equally into a sham-operation group, an intestinal I/R group and an intestinal I/R group pretreated with EGCG intraperitoneally. Light microscopy and transmission electron microscopy examinations showed that I/R induces significant lung injury; however, animals treated with EGCG gives protection of lung parenchyma [124]. In another study, Dona et al. [7] investigated the effect of EGCG on pulmonary fibrosis in neutrophil in mice model. Micromolar EGCG represses reactive oxygen species activity and inhibits apoptosis of activated neutrophils and significantly inhibits chemokine-induced neutrophil chemotaxis in vitro. In another way, oral administration of EGCG blocks neutrophil-mediated angiogenesis in vivo in an inflammatory angiogenesis model and enhances resolution in a pulmonary inflammation model leading to reduce fibrosis. In a recent study, it has been shown that EGCG pretreatment ameliorate seawater aspiration-induced acute lung injury (ALI). EGCG pretreatment has been shown to reduce the total and the phosphorylated protein level of STAT1 in vivo and in vitro and decreased the phosphorylated protein level of JAK1 and JAK2 and thereby ameliorates seawater aspiration-induced ALI [125].

1.7. EGCG and neurodegenerative disease

Neurodegenerative diseases are defined as hereditary (caused by genetically) and sporadic (caused by environmental factor) conditions which are characterized by progressive nervous system dysfunction resulting in the loss of memory and learning. These disorders are often associated with atrophy of the affected central or peripheral structures of the nervous system which includes Alzheimer's disease (AD) and Parkinson's disease (PD). The neuroprotective effects of tea polyphenols have been demonstrated in several studies and it has been suggested that tea consumption is inversely correlated with the incidence of dementia, AD and PD. This may explain why there are significantly lower rates of age-related neurological disorders among Asians than in Europeans or Americans [126]. In a study among a Japanese population, it has been demonstrated that consumption of 2 or more cups/day (100 ml/cup) of green tea is associated with lower prevalence of cognitive impairment [127]. These findings emphasize the importance of well designed controlled studies to assess risk reduction for neurodegenerative diseases in consumers of green tea.

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized clinically by poor onset of memory and cognition impairment, emergence of psychiatric symptoms and behavioral disorders, and impairment of daily living activities. It is the most common form of dementia found in the elderly. During the past decade, many hypotheses have been put forward for AD pathogenesis. Among them, the β-amyloid (Aβ) cascade has widely been accepted. One of the hallmarks of AD is the presence of senile plaques in the hippocampus formed by the deposition of Aβ, which is a 40–42 amino acid polypeptide. The Aβ is made from the amyloid precursor protein (APP) by sequential proteolysis by the two enzymes, β- and γ-secretase, at the N- and C-terminus of the Aβ sequence respectively. However, APP is also processed by α-secretase within the Aβ sequence generating a soluble neurotrophic APPα (APPα). There is growing evidence suggesting that Aβ is a neurotoxin whose aggregation leads to oxidative stress, neuronal destruction and finally the clinical symptoms of AD. Research following this hypothesis suggested that the prevention of AD can be made by decreasing the production of Aβ directly by the cleavage of APP or indirectly by the production of APP, stimulation of clearance of Aβ formed or prevention of aggregation of amyloid plaques. Research with tea polyphenolic compound, mainly EGCG in AD model is currently gained much importance. Recent research investigated the effect and mechanism of EGCG on the degeneretive changes of the brain in AD model mice induced with the drug, D-gal (N-Methylindolyl-β-D-galactopyranoside). EGCG at 6 mg/kg/d for 4 weeks significantly reduced the expression of Aβ and APP in the hippocampus of AD model mice induced by D-gal and prevents neuronal injury [128]. Sommer et al. [129] indicated in their study that irradiation with moderate levels of 670 nm light and EGCG supplementation complementarily reduces Aβ aggregates in human neuroblastoma (SH-EP) cells. Fernandez et al. [130] explored the effect of EGCG on AD mice and suggested that increased non-amyloidogenic processing of APP through the α-secretase and metallopeptidase domain 10 (ADAM10). This study also demonstrated that EGCG-mediated enhancement of non-amyloidogenic processing of APP is mediated by the maturation of ADAM10 via an estrogen receptor-α (ERα)/phosphoinositide 3-kinase (PI3K)/Akt dependent mechanism, but independent of furin-mediated ADAM10 activation. This study indicated that central selective ER modulation could be a therapeutic target for AD and EGCG could be useful in the treatment of this disease. Another study suggested that EGCG could inhibit the activation of ERK and NFκB in the Aβ-injected mouse brains and subsequently suppresses β- and γ-secretases activities and inhibited Aβ-induced apoptotic neuronal cell death leading to amelioration of cognitive dysfunction [131]. EGCG has also been shown to prevent lipopolysaccharide-induced elevation of Aβ production and improves memory deficiency in a mice model [132]. The role of EGCG has been investigated in the Tg2576 AD mouse model in which it was shown to decrease Aβ levels by promoting increased APP cleavage through activation of α-secretase [133]. Rezai-Zadeh et al. [134] showed that a transgenic mice overproducing Aβ treated with EGCG decreased Aβ levels and plaques associated with promotion of the nonamyloidogenic α-secretase proteolytic pathway. Additionally, oral administration of EGCG (50 mg/kg/daily for 6 months) in AD mice model resulted in decreased levels of soluble and insoluble oligomeric Aβ, as well as amelioration of spatial learning deficits [135]. These above data lend credence to the possibility that EGCG as a dietary supplementation could be effective prophylaxis for AD.

Parkinson's disease (PD), like AD, is another severe neurodegenerative disease found in elder population. PD is linked genetically and neuropathologically to α-synuclein and characterized by the accumulation of α-synuclein protein in the brain in the form of lewy bodies. In regard to the relation between PD and tea, it has been suggested that tea consumption is inversely associated with the progression of PD. A case-control study in the United States indicated that people who consumed 2 cups/day or more of tea presented a decreased risk of PD [136]. In support of this finding, another study taken with nearly 30,000 Finnish adults aged 25–74 year followed for 13 year found that drinking 3 or more cups (200 ml/cup) of tea is associated with a reduced risk of PD [137]. A recent study demonstrated that EGCG has been shown to redirect the aggregation of α-synuclein monomers and remodel α-synuclein amyloid fibrils into disordered oligomers [138]. Another recent study indicated that EGCG prevents differentiated SH-SY5Y cells from toxicity induced by 6-hydroxydopamine [139]. Choi et al. [140] demonstrated that both the oral administration of tea and EGCG prevented the loss of tyrosine hydroxylase (TH)-positive cells in the substantia nigra (SN) and the TH activity in the striatum. These treatments also preserved striatal levels of dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid and homovanillic acid (HVA). Thus, EGCG could be a successful dietary supplementation in the prevention of PD.

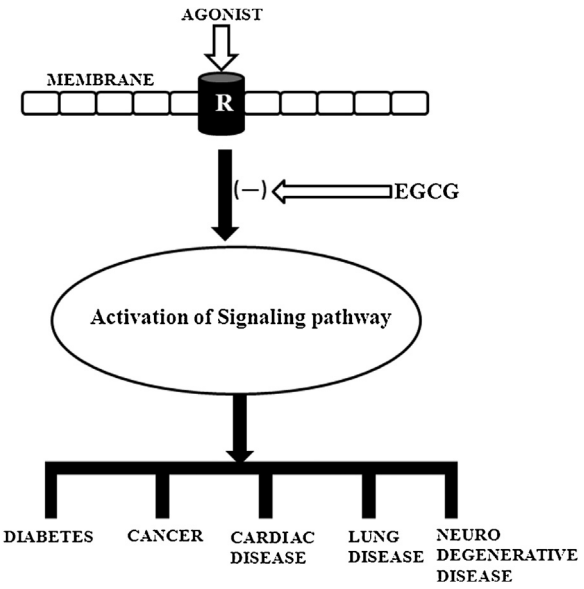

Fig. 3. Role of EGCG in prevention of chronic diseases. Agonist binding to the receptor (R) in the cell membrane leads to activation of various signaling pathways which induces in progression of many chronic diseases, such as cancer, cardiovascular diseases, neurodegenerative disorder. The (−) sign describes that EGCG treatment inhibits agonist induced signaling pathway activation leading to prevention of developing such diseases.

2. Conclusion and future direction

Polyphenols are found abundantly in plants and as a result are consumed in relatively high quantities in the human diet. Over the last 25 years, a considerable amount of data has come into sight with regard to the potential health beneficial effects of several classes of polyphenolic compounds. Tea is a popular beverage containing high amount of polyphenols among which EGCG has been given an important attention for its role in ameliorating various types of disease. Now, the mechanisms by which polyphenols, mainly EGCG, exert such benefits are beginning to be uncovered. The mechanisms involve interactions with a number of cellular signaling pathways, which are important for normal cellular functions. Such interactions appear to modify these signaling pathways, which in turn prevent progression of chronic diseases. However, a better understanding of how EGCG interact with cells, its cellular targets and exact mechanism (s) of action remains to be established.

Molecular dynamics assay on EGCG indicated that 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 important information contributes in elucidating the mechanisms by which tea catechin derivatives act as novel chemopreventive agents. Indeed, EGCG and green tea are potent inhibitors and are orally available pharmacological agents that may be effective in preventing various types of disease such as cancer, heart and neurodegenerative diseases. Fig. 3 schematically represents the role that EGCG plays in prevention of chronic diseases.

Conflict of interest

The authors have declared that there is no conflict of interest.

Acknowledgement

Financial assistance from theCouncil for Industrial Research (CSIR), Govt of India is greatly acknowledged.

References

[1] Y. Kuroda, Y. Hara, Antimutagenic and anticarcinogenic activity of tea polyphenols, Mutat. Res. 436 (1999) 69–97.
[2] H.N. Graham, Green tea composition, consumption and polyphenol chemistry, Prev. Med. 21 (1992) 334–350.
[3] S.C. Langley-Evans, Antioxidant potential of green and black tea determined using the ferric reducing power assay (FRAP), Int. J. Food Sci. Nutr. 51 (2000) 181–188.
[4] D.L. McKay, J.B. Blumberg, The role of tea in human health: An update, J. Am. Coll. Nutr. 21 (2002) 1–13.
[5] K.T. Kavanagh, L.J. Hafer, D.W. Kim, K.K. Mann, D.H. Sherr, A.E. Rogers, G.E. Sonenshein, Green tea extracts decrease carcinogen-induced mammary tumor burden in rats and rate of breast cancer cell proliferation in culture, J. Cell. Biochem. 82 (2001) 387–398.
[6] N. Sueoka, M. Suganuma, E. Sueoka, S. Okabe, S. Matsuyama, K. Imai, K. Nakachi, H. Fujiki, A new function of green tea: prevention of life style related diseases, Ann. N.Y. Acad. Sci. 928 (2001) 274–280.
[7] M. Dona, I. Dell'Aica, F. Calabrese, R. Benelli, M. Morini, A. Albini, S. Garbisa, Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis, J. Immunol. 170 (2003) 4335–4341.
[8] T.M. Haqqi, D.D. Anthony, S. Gupta, N. Ahmad, M.S. Lee, G.K. Kumar, H. Mukhtar, Prevention of collagen-induced arthritis in mice by a polyphenolic fraction from green tea, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 4524–4529.
[9] A.R. Sudano, A.R. Blanco, F. Giuliano, D. Rusciano, V. Enea, Epigallocatechin-gallate enhances the activity of tetracycline in staphylococci by inhibiting its efflux from bacterial cells, Antimicrob. Agents Chemother. 48 (2004) 1968–1973.
[10] M.R. Sartippour, Z.M. Shao, D. Heber, P. Beatty, L. Zhang, C. Liu, L. Ellis, W. Liu, V.L. Go, M.N. Brooks, Green tea inhibits vascular endothelial growth factor (VEGF) induction in human breast cancer cells, J. Nutr. 132 (2002) 2307–2311.
[11] K. Osada, M. Takahashi, S. Hoshina, M. Nakamura, S. Nakamura, M. Sugano, Tea catechins inhibit cholesterol oxidation accompanying oxidation of low density lipoprotein in vitro, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 128 (2001) 153–164.
[12] J.M. Weber, A. Ruzindana-Umunyana, L. Imbeault, S. Sircar, Inhibition of adenovirus infection and adenain by green tea catechins, Antiviral Res. 58 (2003) 167–173.
[13] O. Weinreb, S. Mandel, T. Amit, M.B.H. Youdim, Neurological mechanisms of green tea polyphenols in Alzheimer's and Parkinson's diseases, J. Nutr. Biochem. 15 (2004) 506–516.
[14] D.G. Raederstorff, M.F. Schlachter, V. Elste, P. Weber, Effect of EGCG on lipid absorption and plasma lipid levels in rats, J. Nutr. Biochem. 14 (2003) 326–332.
[15] H. Mukhtar, N. Ahmad, Tea polyphenols: prevention of cancer and optimizing health, Am. J. Clin. Nutr. 71 (2000) 1698–1704.
[16] R.A. Riemersma, C.A. Rice-Evans, R.M. Tyrrell, M.N. Clifford, M.E. Lean, Tea flavonoids and cardiovascular health, Q. J. Med. 94 (2001) 277–282.
[17] J.A. Vinson, Black and green tea and heart disease: a review, Biofactors 13 (2000) 127–132.
[18] M. Sano, M. Tabata, M. Suzuki, M. Degawa, T. Miyase, M. Maeda-Yamamoto, Simultaneous deermination of twelve tea catechins by highperformance liquid chromatography with electrochemical detection, Analyst 126 (2001) 816–820.
[19] J.V. Higdon, B. Frei, Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions, Crit. Rev. Food Sci. Nutr. 43 (2003) 89–143.
[20] C. Vanessa, W. Gary, A Review of the health effects of green tea catechins in in vivo animal models, J . Nutr. 134 (2004) 3431–3440.
[21] P.V. Babu, K.E. Sabitha, C.S. Shyamaladevi, Therapeutic effect of green tea extract on oxidative stress in aorta and heart of streptozotocin diabetic rats, Chem. Biol. Interact. 162 (2006) 114–120.
[22] K. Unno, F. Takabayashi, H. Yoshida, D. Choba, R. Fukutomi, N. Kikunaga, T. Kishido, N. Oku, M. Hoshino, Daily consumption of green tea catechin delays memory regression in aged mice, Biogerontology 8 (2007) 89–95.
[23] M.W. Roomi, V. Ivanov, T. Kalinovsky, A. Niedzwiecki, M. RathIn, In vitro and in vivo antitumorigenic activity of a mixture of lysine proline, ascorbic acid, and green tea extract on human breast cancer lines MDA-MB-231 and MCF-7, Med. Oncol. 22 (2007) 129–138.
[24] S. Khokhar, S.G. Magnusdottir, Total phenol, catechin, and caffeine contents of teas commonly consumed in the United Kingdom, J. Agric. Food Chem. 50 (2002) 565–570.
[25] P.L. Fernandez, M.J. Martin, A.G. Gonzalez, F. Pablos, HPLC determination of catechins and caffeine in tea. Differentiation of green, black and instant teas, Analyst 125 (2000) 421–425.
[26] Z.Y. Chen, Q.Y. Zhu, D. Tsang, Y. Huang, Degradation of green tea catechins in tea drinks, J. Agr. Food Chem. 49 (2001) 477–482.
[27] Z.Y. Chen, Q.Y. Zhu, Y.F. Wong, Z. Zhang, H.Y. Chung, Stabilizing effect of ascorbic acid on green tea catechins, J. Agr. Food Chem. 46 (1998) 2512–2516.
[28] S. Mandel, O. Weinreb, T. Amit, M.B. Youdim, Cell signaling pathways in the neuroprotective actions of the green tea polyphenol(−)-epigallocatechin- 3-gallate: implications for neurodegenerative diseases, J. Neurochem. 88 (2004) 1555–1569.

[29] S.B. Moyers, N.B. Kumar, Green tea polyphenols and cancer chemoprevention: multiple mechanisms and endpoints for phase II trials, Nutr. Rev. 62 (2004) 204–211.
[30] Y.H. Kao, H.H. Chang, M.J. Lee, C.L. Chen, Tea, obesity, and diabetes, Mol. Nutr. Food Res. 50 (2006) 188–210.
[31] Y. Shoji, H. Nakashima, Glucose-lowering effect of powder formulation of African black tea extract in KK-A(y)/TaJcl diabetic mouse, Arch. Pharmacol. Res. 29 (2006) 786–794.
[32] S.M. Chacko, P.T. Thambi, R. Kuttan, I. Nishigaki, Beneficial effects of green tea: a literature review, Chin. Med. 5 (2010) 13.
[33] S. Klaus, S. Pultz, C. Thone-Reineke, S. Wolfram, Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation, Int. J. Obes. 29 (2005) 615–623.
[34] S. Wolfram, D. Raederstorff, M. Preller, Y. Wang, S.R. Teixeira, C. Riegger, P. Weber, Epigallocatechin gallate supplementation alleviates diabetes in rodentsm, J. Nutr. 136 (2006) 2512–2518.
[35] H. Ortsäter, N. Grankvist, S. Wolfram, N. Kuehn, A. Sjöholm, Diet supplementation with green tea extract epigallocatechin gallate prevents progression to glucose intolerance in db/db mice, Nutr. Metab. 9 (2012) 11.
[36] N. Yamabe, T. Yokozawa, T. Oya, M. Kim, Therapeutic potential of (−)-epigallocatechin 3-O-gallate on renal damage in diabetic nephropathy model rats, J. Pharmacol. Exp. Ther. 319 (2006) 228–236.
[37] M.E. Waltner-Law, X.L. Wang, B.K. Law, R.K. Hall, M. Nawano, Granner DK Epigallocatecin gallate a constituent of green tea, represses hepatic glucose production, J. Biol. Chem. 277 (2002) 34933–34940.
[38] H. Tsuneki, M. Ishizuka, M. Terasawa, J.B. Wu, T. Sasaoka, I. Kimura, Effect of green tea on blood glucose levels and serum proteomic patterns in diabetic (db/db) mice and on glucose metabolism in healthy humans, BMC Pharmacol. 4 (2004) 18–21.
[39] L.Y. Wu, C.C. Juan, L.S. Hwang, Y.P. Hsu, P.H. Ho, L.T. Ho, Green tea supplementation ameliorates insulin resistance and increases glucose transporter IV content in a fructose-fed rat model, Eur. J. Nutr. 43 (2004) 116–124.
[40] M.K. Han, Epigallocatechin gallate, a constituent of green tea, suppresses cytokine-induced pancreatic beta-cell damage, Exp. Mol. Med. 35 (2003) 136–139.
[41] E.K. Song, H. Hur, M.K. Han, Epigallocatechin gallate prevents autoimmune diabetes induced by multiple low doses of streptozotocin in mice, Arch. Pharm. Res. 26 (2003) 559–563.
[42] J.D. Lambert, M.J. Lee, H. Lu, X. Meng, J.J.J. Hong, D.N. Seril, M.G. Sturgill, C.S. Yang, Epigallocatechin-3-gallate is absorbed but extensively glucuronidated following oral administration to mice, J. Nutr. 133 (2003) 4172–4177.
[43] U. Ullmann, J. Haller, J.P. Decourt, N. Girault, J. Girault, A.S. Richard-Caudron, B. Pineau, P. Weber, A single ascending dose study of epigallocatechin gallate in healthy volunteers, J. Int. Med. Res. 31 (2003) 88–101.
[44] P.F. Hung, B.T. Wu, H.C. Chen, Y.H. Chen, C.L. Chen, M.H. Wu, H.C. Liu, M.J. Lee, Y.H. Kao, Antimitogenic effect of green tea (−)-epigallocatechin gallate on 3T3-L1 preadipocytes depends on the ERK and Cdk2 pathways, Am. J. Physiol. Cell Physiol. 288 (2005) 1094–1108.
[45] B.T. Wu, P.F. Hung, H.C. Chen, R.N. Huang, H.H. Chang, Y.H. Kao, The apoptotic effect of green tea (−)-epigallocatechin gallateon 3T3-L1 preadipocytes depends on the Cdk2 pathway, J. Agric. Food Chem. 53 (2005) 5695–5701.
[46] C.T. Wang, H.H. Chang, C.H. Hsiao, M.J. Lee, H.C. Ku, Y.J. Hu, Y.H. Kao, The effects of green tea (−)-epigallocatechin-3-gallate on reactive oxygen species in 3T3-L1 preadipocytes and adipocytes depend on the glutathione and 67kDa laminin receptor pathways, Mol. Nutr. Food Res. 53 (2009) 349–360.
[47] K. Mukai, S. Nagai, K. Ohara, Kinetic study of the quenchingreaction of singlet oxygen by tea catechins in ethanolsolution, Free Radic. Biol. Med. 39 (2005) 752–761.
[48] Y. Kobayashi, M. Suzuki, H. Satsu, S. Arai, Y. Hara, K. Suzuki, Y. Miyamoto, M. Shimizu, Green tea polyphenols inhibit the sodium-dependent glucose transporter of intestinal epithelial cells by a competitive mechanism, J. Agric. Food Chem. 48 (2000) 5618–5623.
[49] Q. Yang, T.E. Graham, N. Mody, F. Preitner, O.D. Peroni, J.M. Zabolotny, K. Kotani, L. Quadro, B.B. Kahn, Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes, Nature 436 (2005) 356–362.
[50] M.A. Herman, B.B. Kahn, Glucose transport and sensing in the maintenance of glucose homeostasis and metabolic harmony, J. Clin. Invest. 116 (2006) 1767–1775.
[51] J.H. Park, J.H. Bae, S.S. Im, D.K. Song, Green tea and type 2 diabetes, Integr. Med. Res. 3 (2014) 4–10.
[52] R. Artali, G. Beretta, P. Morazzoni, E. Bombardelli, F. Meneghetti, Green tea catechins in chemoprevention of cancer: a molecular docking investigation into their interaction with glutathione S-transferase (GST P1-1), J. Enzyme Inhib. Med. Chem. 24 (2009) 287–295.
[53] C.D. Mann, C.P. Neal, G. Garcea, M.M. Manson, A.R. Dennison, D.P. Berry, Phytochemicals as potential chemopreventive and chemotherapeutic agents in hepatocarcinogenesis, Eur. J. Cancer Prev. 18 (2009) 13–25.
[54] Y.C. Kuo, C.L. Yu, C.Y. Liu, S.F. Wang, P.C. Pan, M.T. Wu, C.K. Ho, Y.S. Lo, Y. Li, D.C. Christiani, A population-based, case-control study of green tea consumption and leukemia risk in southwestern Taiwan, Cancer Causes Control 20 (2009) 57–65.
[55] D. Chen, V. Milacic, M.S. Chen, S.B. Wan, W.H. Lam, C. Huo, K.R. Landis-Piwowar, Q.C. Cui, A. Wali, T.H. Chan, Q.P. Dou, Tea polyphenols, their biological effects and potential molecular targets, Histol. Histopathol. 23 (2008) 487–496.
[56] J. Steevens, L.J. Schouten, B.A. Verhage, R.A. Goldbohm, P.A. van den Brandt, Tea and coffee drinking and ovarian cancer risk: results from the Netherlands cohort study and a meta-analysis, Br. J. Cancer 97 (2007) 1291–1294.
[57] N. Kurahashi, S. Sasazuki, M. Iwasaki, M. Inoue, S. Tsugane, Green tea consumption and prostate cancer risk in Japanese men: a prospective study, Am. J. Epidemiol. 167 (2008) 71–77.
[58] D.N. Syed, N. Khan, F. Afaq, H. Mukhtar, Chemoprevention of prostate cancer through dietary agents: progress and promise, Cancer Epidemiol. Biomarkers Prev. 16 (2007) 2193–2203.
[59] W. Liang, C.W. Binns, L. Jian, A.H. Lee, Does the consumption of green tea reduce the risk of lung cancer among smokers? Evid. Based Complement. Alternat. Med. 4 (2007) 17–22.
[60] J. Ju, J. Hong, J.N. Zhou, Z. Pan, M. Bose, J. Liao, G.Y. Yang, Y.Y. Liu, Z. Hou, Y. Lin, J. Ma, W.J. Shih, A.M. Carothers, C.S. Yang, Inhibition of intestinal tumorigenesis in Apcmin/+ mice by (-)-pigallocatechin-3-gallate, the major catechin in green tea, Cancer. Res. 65 (2005) 10623–10631.
[61] M. Shimizu, A. Deguchi, Y. Hara, H. Moriwaki, I.B. Weinstein, EGCG inhibits activation of the insulin-like growth factor-1 receptor in human colon cancer cells, Biochem. Biophys. Res. Commun. 334 (2005) 947–953.
[62] C.S. Yang, X. Wang, G. Lu, S.C. Picinich, Cancer prevention by tea: animal studies, molecular mechanisms and human relevance, Nat. Rev. Cancer 9 (2009) 429–439.
[63] C.S. Yang, H. Wang, G.X. Li, Z. Yang, F. Guan, H. Jin, Cancer prevention by tea: Evidence from laboratory studies, Pharmacol. Res. 64 (2011) 113–122.
[64] C.L. Sun, J.M. Yuan, W.P. Koh, M.C. Yu, Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies, Carcinogenesis 27 (2006) 1301–1309.
[65] S. Bettuzzi, M. Brausi, F. Rizzi, G. Castagnetti, G. Peracchia, A. Corti, Chemoprevention of human prostate cancer by oral administration of green tea catechins in volunteers with high-grade prostate intraepithelial neoplasia: a preliminary report from a one-year proof-of-principle study, Cancer Res. 66 (2006) 1234–1240.
[66] F. Farabegoli, C. Barbi, E. Lambertini, R. Piva, (−)-Epigallocatechin-3-gallate downregulates estrogen receptor alpha function in MCF-7 breast carcinoma cells, Cancer Detect. Prev. 31 (2007) 499–504.
[67] R.L. Thangapazham, N. Passi, R.K. Maheshwari, Green tea polyphenol and epigallocatechin gallate induce apoptosis and inhibit invasion in human breast cancer cells, Cancer Biol. Ther. 6 (2007) 1938–1943.
[68] S. Shankar, S. Ganapathy, S.R. Hingorani, R.K. Srivastava, EGCG inhibits growth, invasion, angiogenesis and metastasis of pancreatic cancer, Front. Biosci. 13 (2008) 440–452.
[69] Y.C. Ho, S.F. Yang, C.Y. Peng, M.Y. Chou, Y.C. Chang, Epigallocatechin-3-gallate inhibits the invasion of human oral cancer cells and decreases the productions of matrix metalloproteinases and urokinase-plasminogen activator, J. Oral Pathol. Med. 36 (2007) 588–593.
[70] M. Kim, A. Murakami, H. Ohigashi, Modifying effects of dietary factors on (−)-epigallocatechin-3-gallate-induced pro-matrix metalloproteinase-7 production in HT-29 human colorectal cancer cells, Biosci. Biotechnol. Biochem. 71 (2007) 2442–2450.
[71] I.A. Siddiqui, A. Malik, V.M. Adhami, M. Asim, B.B. Hafeez, S. Sarfaraz, H. Mukhtar, Green tea polyphenol EGCG sensitizes human prostate carcinoma LNCaP cells to TRAIL-mediated poptosis and synergistically inhibits biomarkers associated with angiogenesis and metastasis, Oncogene 27 (2008) 2055–2063.
[72] H.N. Yu, S.R. Shen, J.J. Yin, Effects of metal ions, catechins, and their interactions on prostate cancer, Crit. Rev. Food Sci. Nutr. 47 (2007) 711–719.
[73] N. Khan, H. Mukhtar, Multitargeted therapy of cancer by green tea polyphenols, Cancer Lett. 269 (2008) 269–280.
[74] T. Yamamoto, S. Hsu, J. Lewis, J. Wataha, D. Dickinson, B. Singh, W.B. Bollag, P. Lockwood, E. Ueta, T. Osaki, G. Schuster, Green tea polyphenols causes differential oxidative environments in tumor versus normal epithelial cells, J. Pharmacol. Exp. Ther. 301 (2003) 230–236.
[75] K. Nakachi, S. Matsuyama, S. Miyake, M. Suganuma, K. Imai, Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention, Biofactors 13 (2000) 49–54.
[76] M. Inoue, K. Tajima, M. Mizutani, H. Iwata, T. Iwase, S. Miura, K. Hirose, N. Hamajima, S. Tomonaga, Regular consumption of green tea and the risk of breast cancer recurrence: follow-up study from the hospital-based epidemiologic research program at Aichi cancer center (HERPACC), Japan, Cancer Lett. 167 (2001) 175–182.
[77] S.S. Chung, J.V. Vadgama, Curcumin and epigallocatechin gallate inhibit the cancer stem cell phenotype via down-regulation of STAT3-NFκB signaling, Anticancer Res. 35 (2015) 39–46.
[78] S. Wang, R. Chen, Z. Zhong, Z. Shi, M. Chen, Y. Wang, Epigallocatechin-3-gallate potentiates the effect of curcumin in inducing growth inhibition and apoptosis of resistant breast cancer cells, Am. J. Chin. Med. 42 (2014) 1279–1300.
[79] H.Q. Luo, M. Xu, W.T. Zhong, Z.Y. Cui, F.M. Liu, K.Y. Zhou, X.Y. Li, EGCG decreases the expression of HIF-1α and VEGF and cell growth in MCF-7 breast cancer cells, J. BUON 19 (2014) 435–439.
[80] C. Braicu, C.D. Gherman, A. Irimie, I. Berindan-Neagoe, Epigallocatechin-3-Gallate (EGCG) inhibits cell proliferation and migratory behaviour of triple negative breast cancer cells, J. Nanosci. Nanotechnol. 13 (2013) 632–637.

[81] A.B. Awad, S.L. Barta, C.S. Fink, P.G. Bradford, Beta-sitosterol enhances tamoxifen effectiveness on breast cancer cells by affecting ceramide metabolism, Mol. Nutr. Food Res. 52 (2008) 419–426.
[82] H.C. Huang, T.D. Way, C.L. Lin, J.K. Lin, EGCG stabilizes p27kip1 in E2-stimulated MCF-7 cells through down-regulation of the Skp2 protein, Endocrinology 149 (2008) 5972–5983.
[83] J.R. Zhou, L.Y. Yu, Z.M. Mai, G.L. Blackburn, Combined inhibition of estrogendependent human breast carcinoma by soy and tea bioactive components in mice, Int. J. Cancer 108 (2004) 8–14.
[84] J. Kanwar, M. Taskeen, I. Mohammad, C. Huo, T.H. Chan, Q.P. Dou, Recent advances on tea polyphenols, Front. Biosci (Elite Ed). 4 (2012) 111–131.
[85] A. Komori, J. Yatsunami, S. Okabe, S. Abe, K. Hara, M. Suganuma, S.J. Kim, H. Fujiki, Anticarcinogenic activity of green tea polyphenols, Jpn. J. Clin. Oncol. 23 (1993) 186–190.
[86] M.M. Cromie, W. Gao, Epigallocatechin-3-gallate enhances the therapeutic effects of leptomycin B on human lung cancer a549 cells, Oxid. Med. Cell. Longev 2015 (2015) 217304.
[87] J. Shi, F. Liu, W. Zhang, X. Liu, B. Lin, X. Tang, Epigallocatechin-3-gallate inhibits nicotine-induced migration and invasion by the suppression of angiogenesis and epithelial-mesenchymal transition in non-small cell lung cancer cells, Oncol. Rep. 33 (2015) 2972–2980.
[88] J.I. Sonoda, R. Ikeda, Y. Baba, K. Narumi, A. Kawachi, E. Tomishige, K. Nishihara, Y. Takeda, K. Yamada, K. Sato, T. Motoya, Green tea catechin, epigallocatechin-3-gallate, attenuates the cell viability of human non-small-cell lung cancer A549 cells via reducing Bcl-xL expression, Exp. Ther. Med. 8 (2014) 59–63.
[89] K.C. Kim, C. Lee, Reversal of cisplatin resistance by epigallocatechin gallate is mediated by downregulation of axl and tyro 3 expressions in human lung cancer cells, Korean J. Physiol. Pharmacol. 18 (2014) 61–66.
[90] J.H. Shim, Z.Y. Su, J.I. Chae, D.J. Kim, F. Zhu, W.Y. Ma, A.M. Bode, C.S. Yang, Z. Dong, Epigallocatechin gallate suppresses lung cancer cell growth through Ras-GTPase-activating protein SH3 domain-binding protein 1, Cancer Prev. Res. 3 (2010) 670–679.
[91] Y.C. Ma, C. Li, F. Gao, Y. Xu, Z.B. Jiang, J.X. Liu, L.Y. Jin, Epigallocatechin gallate inhibits the growth of human lung cancer by directly targeting the EGFR signaling pathway, Oncol. Rep. 31 (2014) 1343–1349.
[92] Y. Sakamoto, N. Terashita, T. Muraguchi, T. Fukusato, S. Kubota, Effects of epigallocatechin-3-gallate (EGCG) on A549 lung cancer tumor growth and angiogenesis, Biosci. Biotechnol. Biochem. 77 (2013) 1799–1803.
[93] X. Li, Y. Feng, J. Liu, X. Feng, K. Zhou, X. Tang, Epigallocatechin-3-gallate inhibits IGF-I-stimulated lung cancer angiogenesis through downregulation of HIF-1α and VEGF expression, J. Nutrigenet. Nutrigenomics 6 (2013) 169–178.
[94] L. Jin, C. Li, Y. Xu, L. Wang, J. Liu, D. Wang, C. Hong, Z. Jiang, Y. Ma, Q. Chen, F. Yu, Epigallocatechin gallate promotes p53 accumulation and activity via the inhibition of MDM2-mediated p53 ubiquitination in human lung cancer cells, Oncol. Rep. 29 (2013) 1983–1990.
[95] H. Ko, Y. So, H. Jeon, M.H. Jeong, H.K. Choi, S.H. Ryu, S.W. Lee, H.G. Yoon, K.C. Choi, TGF-β1-induced epithelial-mesenchymal transition and acetylation of Smad2 and Smad3 are negatively regulated by EGCG in human A549 lung cancer cells, Cancer Lett. 335 (2013) 205–213.
[96] Y.T. Deng, J.K. Lin, EGCG inhibits the invasion of highly invasive CL1-5 lung cancer cells through suppressing MMP-2 expression via JNK signaling and induces G2/M arrest, J. Agric. Food Chem. 59 (2011) 13318–13327.
[97] S. Gupta, K. Hastak, N. Ahmad, J.S. Lewin, H. Mukhtar, Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 10350–10355.
[98] V.M. Adhami, I.A. Siddiqui, N. Ahmad, S. Gupta, H. Mukhtar, Oral consumption of green tea polyphenols inhibits insulin-like growth factor-I-induced signaling in an autochthonous mouse model of prostate cancer, Cancer Res. 64 (2004) 8715–8722.
[99] A.G. Paschka, R. Butler, C.Y. Young, Induction of apoptosis in prostate cancer cell lines by the green tea component, (−)-epigallocatechin-3-gallate, Cancer Lett. 130 (1998) 1–7.
[100] K. Brusselmans, S.E. De, W. Heyns, G. Verhoeven, J.V. Swinnen, Epigallocatechin-3-gallate is a potent natural inhibitor of fatty acid synthase in intact cells and selectively induces apoptosis in prostate cancer cells, Int. J. Cancer 106 (2003) 856–862.
[101] S.K. Katiyar, R. Agarwal, Z.Y. Wang, A.K. Bhatia, H. Mukhtar, (−)-Epigallocatechin-3-gallate in Camellia sinensis leaves from himalayan region of Sikkim: inhibitory effects against biochemical events and tumor initiation in SENCAR mouse skin, Nutr. Cancer 18 (1992) 73–83.
[102] U. Peters, C. Poole, L. Arab, Does tea affect cardiovascular disease? A meta-analysis, Am. J. Epidemiol. 154 (2001) 495–503.
[103] L.B.M. Tijburg, T. Mattern, J.D. Folts, U.M. Weisgerber, M.B. Katan, Tea flavonoids and cardiovascular diseases: a review, Food Sci. Nutr. 37 (1997) 771–785.
[104] W. Young, R.L. Hotovec, A.G. Romero, Tea and atherosclerosis, Nature 216 (1967) 1015–1016.
[105] L. Fu-quing, Z. Mei-fang, Z. Xiao-gang, L. Ji-min, Y. Wei-long, A study on tea-pigment in prevention of atherosclerosis, Chin. Med. J. 102 (1989) 579–583.
[106] L.B.M. Tijburg, S.A. Wiseman, G.W. Meijer, J.A. Weststrate, Effects of green tea, black tea and dietary lipophilic antioxidants on LDL oxidizability and atherosclerosis in hypercholesterolemic rabbits, Atherosclerosis 135 (1997) 37–47.
[107] Z. Hong, Y. Xu, J.F. Yin, J. Jin, Y. Jiang, Q. Du, Improving the effectiveness of (−)-epigallocatechin gallate (EGCG) against rabbit atherosclerosis by EGCG-loaded nanoparticles prepared from chitosan and polyaspartic acid, J. Agric. Food Chem. 62 (2014) 12603–12609.
[108] Y. Cai, T. Kurita-Ochiai, T. Hashizume, M. Yamamoto, Green tea epigallocatechin-3-gallate attenuates Porphyromonas gingivalis-induced atherosclerosis, Pathog. Dis. 67 (2013) 76–83.
[109] E. Ramesh, R. Elanchezhian, M. Sakthivel, T. Jayakumar, R.S. Senthil Kumar, P. Geraldine, P.A. Thomas, Epigallocatechin gallate improves serum lipid profile and erythrocyte and cardiac tissue antioxidant parameters in Wistar rats fed an atherogenic diet, Fundam. Clin. Pharmacol. 22 (2008) 275–284.
[110] E. Ramesh, P. Geraldine, P.A. Thomas, Regulatory effect of epigallocatechin gallate on the expression of C-reactive protein and other inflammatory markers in an experimental model of atherosclerosis, Chem. Biol. Interact. 183 (2010) 125–132.
[111] K.Y. Chyu, S.M. Babbidge, X. Zhao, R. Dandillaya, A.G. Rietveld, J. Yano, P. Dimayuga, B. Cercek, P.K. Shah, Differential effects of green tea-derived catechin on developing versus established atherosclerosis in apolipoprotein E-null mice, Circulation 109 (2004) 2448–2453.
[112] S. Wolfram, Effects of green tea and EGCG on cardiovascular and metabolic health, J. Am. Coll. Nutr. 26 (2007) 373–388.
[113] Y. Hotta, L. Huang, T. Muto, M. Yajima, K. Miyazeki, N. Ishikawa, Y. Fukuzawa, Y. Wakida, H. Tushima, H. Ando, T. Nonogaki, Positive inotropic effect of purified green tea catechin derivative in guinea pig hearts: the measurements of cellular Ca2and nitric oxide release, Eur. J. Pharmacol. 552 (2006) 123–130.
[114] R. Aneja, P.W. Hake, T.J. Burroughs, A.G. Denenberg, H.R. Wong, B. Zingarelli, Epigallocatechin a green tea polyphenol, attenuates myocardial ischemia reperfusion injury in rats, Mol. Med. 10 (2004) 55–62.
[115] H.L. Li, Y. Huang, C.N. Zhang, G. Liu, Y.S. Wei, A.B. Wang, Y.Q. Liu, R.T. Hui, C. Wei, G.M. Williams, D.P. Liu, C.C. Liang, Epigallocathechin- 3 gallate inhibits cardiac hypertrophy through blocking reactive oxidative species-dependent and -independent signal pathways, Free Radic. Biol. Med. 40 (2006) 1756–1775.
[116] X. Zeng, X. Tan, Epigallocatechin-3-gallate and zinc provide anti-apoptotic protection against hypoxia/reoxygenation injury in H9c2 rat cardiac myoblast cells, Mol. Med. Rep. 12 (2015) 1850–1856.
[117] M.E. Widlansky, N.M. Hamburg, E. Anter, M. Holbrook, D.F. Kahn, J.G. Elliott, J. F. Keaney, J.A. Vita, Acute EGCG supplementation reverses endothelial dysfunction in patients with coronary artery disease, J. Am. Coll. Nutr. 26 (2007) 95–102.
[118] C. Yao, J. Zhang, G. Liu, F. Chen, Y. Lin, Neuroprotection by (−)-epigallocatechin-3-gallate in a rat model of stroke is mediated through inhibition of endoplasmic reticulum stress, Mol. Med. Rep. 9 (2014) 69–76.
[119] J. Ding, G. Fu, Y. Zhao, Z. Cheng, Y. Chen, B. Zhao, W. He, L.J. Guo, EGCG ameliorates the suppression of long-term potentiation induced by ischemia at the Schaffer collateral-CA1 synapse in the rat, Cell. Mol. Neurobiol. 32 (2012) 267–277.
[120] S.H. Lim, H.S. Kim, Y.K. Kim, T.M. Kim, S. Im, M.E. Chung, B.Y. Hong, Y.J. Ko, H. W. Kim, J.I. Lee, The functional effect of epigallocatechin gallate on ischemic stroke in rats, Acta Neurobiol. Exp. 70 (2010) 40–46.
[121] A.M. Haque, M. Hashimoto, M. Katakura, Y. Hara, O. Shido, Green tea catechins prevent cognitive deficits caused by Abeta1-40 in rats, J. Nutr. Biochem. 19 (2008) 619–626.
[122] M. Suzuki, M. Tabuchi, M. Ikeda, K. Umegaki, T. Tomita, Protective effects of green tea catechins on cerebral ischemic damage, Med. Sci. Monit. 10 (2004) 166–174.
[123] S. Uchida, M. Ozaki, T. Akashi, K. Yamashita, M. Niwa, K. Taniyama, Effects of (−)-epigallocatechin-3-O-gallate (green tea tannin) on the life span of stroke-prone spontaneously hypertensive rats, Clin. Exp. Pharmacol. Physiol. 22 (1995) 302–313.
[124] A.E. Giakoustidis, D.E. Giakoustidis, S. Iliadis, G. Papageorgiou, K. Koliakou, N. Kontos, I. Taitzoglou, E. Botsoglou, V. Papanikolaou, K. Atmatzidis, D. Takoudas, A. Antoniadis, Attenuation of intestinal ischemia/reperfusion induced liver and lung injury by intraperitoneal administration of (−)-epigallocatechin-3-gallate, Free Radic. Res. 40 (2006) 103–110.
[125] W. Liu, M. Dong, L. Bo, C. Li, Q. Liu, Y. Li, L. Ma, Y. Xie, E. Fu, D. Mu, L. Pan, F. Jin, Z. Li, Epigallocatechin-3-gallate ameliorates seawater aspiration-induced acute lung injury via regulating inflammatory cytokines and inhibiting JAK/STAT1 pathway in rats, Mediators Inflamm. 2014 (2014) 612593.
[126] K. Ritchie, S. Lovestone, The dementias, Lancet 360 (2002) 1759–1766.
[127] S. Kuriyama, A. Hozawa, K. Ohmori, T. Shimazu, T. Matsui, S. Ebihara, S. Awata, R. Nagatomi, H. Arai, I. Tsuji, Green tea consumption and cognitive function: a cross-sectional study from the Tsurugaya Project 1, Am. J. Clin. Nutr. 83 (2006) 355–361.
[128] M. He, M.Y. Liu, S. Wang, Q.S. Tang, W.F. Yao, H.S. Zhao, M.J. Wei, Research on EGCG improving the degenerative changes of the brain in AD model mice induced with chemical drugs, Zhong. Yao. Cai. 35 (2012) 1641–1644.
[129] A.P. Sommer, J. Bieschke, R.P. Friedrich, D. Zhu, E.E. Wanker, H.J. Fecht, D. Mereles, W. Hunstein, 670 nm laser light and EGCG complementarily reduce amyloid-β aggregates in human neuroblastoma cells: basis for treatment of Alzheimer's disease? Photomed. Laser Surg. 30 (2012) 54–60.
[130] J.W. Fernandez, K. Rezai-Zadeh, D. Obregon, J. Tan, EGCG functions through estrogen receptor-mediated activation of ADAM10 in the promotion of non-amyloidogenic processing of APP, FEBS Lett. 584 (2010) 4259–4267.

[131] J.W. Lee, Y.K. Lee, J.O. Ban, T.Y. Ha, Y.P. Yun, S.B. Han, K.W. Oh, J.T. Hong, Green tea (−)-epigallocatechin-3-gallate inhibits beta-amyloid-induced cognitive dysfunction through modification of secretase activity via inhibition of ERK and NF-kappaB pathways in mice, J. Nutr. 139 (2009) 1987–1993.
[132] Y.K. Lee, D.Y. Yuk, J.W. Lee, S.Y. Lee, T.Y. Ha, K.W. Oh, Y.P. Yun, J.T. Hong, (−)-Epigallocatechin-3-gallate prevents lipopolysaccharide-induced elevation of beta-amyloid generation and memory deficiency, Brain Res. 1250 (2009) 164–174.
[133] D.F. Obregon, K. Rezai-Zadeh, Y. Bai, N. Sun, H. Hou, J. Ehrhart, J. Zeng, T. Mori, G.W. Arendash, D. Shytle, T. Town, J. Tan, ADAM10 activation is required for green tea (−)- epigallocatechin-3-gallate-induced alpha-secretase cleavage of amyloid precursor protein, J. Biol. Chem. 281 (2006) 16419–16427.
[134] K. Rezai-Zadeh, D. Shytle, N. Sun, T. Mori, H. Hou, D. Jeanniton, J. Ehrhart, K. Townsend, J. Zeng, D. Morgan, J. Hardy, T. Town, J. Tan, Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice, J. Neurosci. 25 (2005) 8807–8814.
[135] K. Rezai-Zadeh, G.W. Arendash, H. Hou, F. Fernandez, M. Jensen, M. Runfeldt, R.D. Shytle, J. Tan, Green tea epigallocatechin-3-gallate (EGCG) reduces beta-amyloid mediated cognitive impairment and modulates tau pathology in Alzheimer transgenic mice, Brain Res. 1214 (2008) 177–187.
[136] H. Checkoway, K. Powers, T. Smith-Weller, G.M. Franklin, W.T. Longstreth, P.D. Swanson, Parkinson's disease risks associated with cigarette smoking, alcohol consumption, and caffeine intake, Am. J. Epidemiol. 155 (2002) 732–738.
[137] G. Hu, S. Bidel, P. Jousilahti, R. Antikainen, J. Tuomilehto, Coffee and tea consumption and the risk of Parkinson's disease, Mov. Disord. 22 (2007) 2242–2248.
[138] N. Lorenzen, S.B. Nielsen, Y. Yoshimura, B.S. Vad, C.B. Andersen, C. Betzer, J.D. Kaspersen, G. Christiansen, J.S. Pedersen, P.H. Jensen, F.A. Mulder, D.E. Otzen, How epigallocatechin gallate can inhibit α-synuclein oligomer toxicity in vitro, J. Biol. Chem. 289 (2014) 21299–21310.
[139] J. Chao, W.K. Lau, M.J. Huie, Y.S. Ho, M.S. Yu, C.S. Lai, M. Wang, W.H. Yuen, W.H. Lam, T.H. Chan, R.C. Chang, A pro-drug of the green tea polyphenol (−)-epigallocatechin-3-gallate (EGCG) prevents differentiated SH-SY5Y cells from toxicity induced by 6-hydroxydopamine, Neurosci. Lett. 469 (2010) 360–364.
[140] J.Y. Choi, C.S. Park, D.J. Kim, M.H. Cho, B.K. Jin, J.E. Pie, W.G. Chung, Prevention of nitric oxide-mediated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease in mice by tea phenolic epigallocatechin 3-gallate, Neurotoxicology 23 (2002) 367–374.