Green tea polyphenols and their potential role in health and disease

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Abstract There is a growing body of evidence that plant polyphenols such as resveratrol, anthocyanins, catechins, and terpenes like taxol are effectively used in the treatment of chronic conditions including cancer, Alzheimer, Parkinsonism, diabetes, aging, etc. The link between oxidative stress and inflammation is well accepted. Thus, the mechanism of action of these natural products is partly believed to be through their significant antioxidant properties. The main constituent of green tea, with clinical significance, is epigallocatechin gallate (EGCG). It has been associated with antitumor, anti-Alzheimer, and anti-aging properties, improve redox status at the tissue level possibly preventing system level structural damage. This review focuses on EGCG and its potential therapeutic role in health and disease.

Graphical abstract

Keywords Green tea · Epigallocatechin gallate · Inflammation · Cancer · Fibrosis · Alzheimer · Parkinsonism · Aging

Introduction

Polyphenols are commonly present at capricious level in all green plants. Phenolic compounds are low molecular weight molecules, widespread in nature and elaborated by fungi, yeast, algae, lichen, prokaryotes, insects, and mammals. In the producer organism, phenolic compounds are present in small amounts but under stress (physical/chemical/biochemical) these compounds are produced in relatively larger amounts. Thus, their role in the organisms is of defense against predators, infection, inflammation, and allelopathic interactions (Bhattacharya et al. 2010).
Natural phenols are mostly water-soluble and can also be volatile materials. These can be classified into many categories including simple monomeric phenols. This may include one or more phenolic hydroxyl functions and/or carboxylic acid groups including cinnamic acid derivatives (C6–C3) with diverse biological activities (Lin et al. 2014; Pontiki et al. 2014). The second group of phenolic compounds may contain more complex molecules with two rings such as coumarins, isocoumarins, stilbens, chalcones, and curcuminoids, with distinct biological activities (Torres et al. 2014; Passamani et al. 2014; Wong and Fiscus 2015; Sharma et al. 2015). Curcuminoids are known potent anticarcinogens (Wright et al. 2013). The third group of phenolic compounds may be more complex such as flavonoids and isoflavonoids, also called bioflavonoids, due to their biological activities (Wright et al. 2013). Phenyl propanoids may also include a large number of catechins, cyanidins, and anthocyanins, the later two classes being responsible for different colors and biological activities of fruits, flowers, and vegetable (Bastos et al. 2015). A comprehensive review is available on flavonoids and major natural polyphenols (Khan et al. 2014).

**Catechins in tea**

Green tea (*Camellia sinensis*, CS.) is a universal beverage and is mostly consumed in China, Southeast Asia, and Japan. In Southeast Asia, its postprandial consumption is believed to metabolize fat (Peluso et al. 2014). However, in Japan and China, green tea extract is prandially consumed and is also believed to help in meat and fat digestion, helping obesity and related health problems.

CS has several, in vitro and in vivo-antimetastasis and osteolytic properties (Luo et al. 2014). The activities of CS may be attributed to the presence of a number of catechins with epigallocatechin-3-gallate (EGCG, Fig. 1) being the major catechin component. Catechins are polyphenolic flavanol molecules derived from C6–C3–C6, shikimate biosynthetic pathway. Other catechins in green tea are epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC) and in black tea polyphenols are theaflavins (TF) and thearubigins (He et al. 2015). Black tea is rich in polysaccharides, while green tea is rich in polyphenols including EGCG (Chen et al. 2009). EGCG is known for its anti-inflammatory, hypoglycemic, hypcholesteremic, anticancer, antihypertensive, antioxidant, antiviral, and pancreatic anticancer activities (Yousaf et al. 2014). Tea extract has been reported to show an inhibitory effect on blood coagulation, prevent the onset of certain type of cardiovascular diseases [atherosclerosis], disolve fibrinogen, inhibit platelet aggregation, (Liatsos et al. 2010) lower endothelin level (Unger 2010), activate GSH-Px, protect LDL oxidation (Wojciech et al. 2010), and improve glucose tolerance in diabetes (Zuo et al. 2014).

**Green tea has anti-inflammatory and anticancer properties**

Oxidative stress/inflammation contributes to tissue injury after hemorrhage/resuscitation, and natural polyphenolic compounds are the drugs of choice for attenuation of injury (Relja et al. 2012). Thus, theaflavin polyphenols from tea and the flavonoid chrysin from *Potentilla evesitita* (Rosaceae) are just two examples of polyphenols with antioxidant, antitumor, and anti-inflammatory activities (Weerawatanakom et al. 2015; Rafi et al. 2015). Polyphenols have also been implicated in many other chronic conditions such as Parkinson disease, Alzheimer’s disease, antinociceptive, immune response, malignancy, anticalcification, hypertension, health and development, etc. (Zhang et al. 2015; Srinivasan and Lahiri 2015; Rahman et al. 2015; Magrone and Jirillo 2015; Signorelli et al. 2015; Wang et al. 2015; Teles et al. 2015; Ly et al. 2015). There is a plethora of information that reflects on the fact that activities of green tea polyphenolic compounds can control chronic diseases that are mediated through persistent inflammation. The role of dietary polyphenols in the management of inflammation is reviewed (Farzael et al. 2015).

The anti-inflammatory activity of polyphenols in green tea extract (GTE) has been demonstrated in various models of acute inflammation (Singh et al. 2010; Relja et al. 2012; Shen et al. 2011, 2012), and numerous mechanisms have been suggested for their anticancer activities including suppression of NF-kappaB, inflammasome, and IL-1beta secretion (Lamoral-Theys et al. 2010; Ellis et al. 2011). Many malignancies are characterized by an activation of interleukin-associated kinases, and several drugs targeting specific kinases, both natural and synthetic, are being used for cancer treatment (Guo et al. 2015; Kim et al. 2015). Polo-like kinase (PLK1) interacts with green tea catechins resulting in growth inhibition of several types on human cancers (Shan et al. 2015). EGCG is a multi-cellular effector that can inhibit development of numerous types of tumors such as lung tumor (Mei et al. 2011) possibly by stabilizing HIF-1 alpha, endometrial adenocarcinoma, and hepatocellular carcinoma (Roomi et al. 2012; Wang et al. 2011).

Synergistic effect of EGCG, in combination drugs, has been extensively studied, and it is claimed that green tea extracts are synergists with anticancer drugs and micronutrients (Niedzwiecki et al. 2010). EGCG also has the ability to sensitize the efficacy of numerous chemotherapy agents such as doxorubicin (DOX) and chrysirin in hepatic carcinoma, gastric cancer, etc. (Chen et al. 2014a; Sun et al. 2011). A preventive role of EGCG in cardiotoxicity induced by DOX has been reported (Li et al. 2010). In addition, EGCG plays a dose-dependent inhibitory role in autophagy signaling and inhibits the cellular growth with a synergistic effect.
(40–60 % increment) on cell death when combined with doxorubicin (Chen et al. 2014a).

This is further confirmed by a combination therapy with rapamycin, an autophagy antagonist which impairs the anticancer effect of either DOX by itself or in combination with EGCG (Chen et al. 2014a). DOX encapsulated in 6-O-(3-hexadecyloxy-2-hydroxypropyl)-hyaluronic acid nanoparticles, 9HDHA-NPs, with EGCG significantly inhibits the growth of Ehrlich ascites tumors (Ray et al. 2013). Further, EGCG in combination with vitamin A or ascorbic acid has been reported to show beneficial effects for B16 melanoma and other types of cancer prevention (Gao et al. 2013; Lee et al. 2010; Wel et al. 2003).

In numerous cell culture studies, EGCG induces apoptosis and suppresses subsequent cell growth in head and neck cancers, human ovarian carcinoma cell lines OVCAR3, multiple myeloma cells, human squamous carcinoma, SiHa human cervical cancer cell, and prostate cancer (Huang et al. 2014; Al-Hazzani and Alshatwi, 2011; Ren et al. 2011; Rao and Pagidas, 2010). It has been demonstrated that EGCG inhibits OVCAR3 cell proliferation by activation of p38 MAPK and down-regulation of protein expression of MMP2. Synergistic effect of EGCG with curcumin for the control of human colon adenocarcinoma (HCT 15, HCT 116) and human larynx carcinoma has been reported (Manikandan et al. 2012). A potential
Mechanism of action of EGCG

EGCG and its underlying mechanism of action have been extensively studied for anticancer activities. EGCG is bio-activated after its conjugation with cysteine to form 2′-cysteiny1-EGCG and 2′′-cysteiny1-EGCG. Both of these products inhibit colon cancer in a dose-dependent manner, and both metabolites prevent arachidonic acid release and nitric oxide production indicating anti-inflammatory and antioxidant activities (Lambert et al. 2010). In addition, several synthetic analogs of EGCG have been prepared to study structure–activity relationship, in order to define potential molecular targets of EGCG (Chen et al. 2011). Thus, several mechanisms of action of EGCG to target cancer progression have been proposed. These include cancer development and progression, invasion, metastasis, chronic inflammation for increased risk of colorectal cancer, suppression of cell de-adhesion/migration, and inhibition of other clinical parameters (Li et al. 2011). An activation of phosphoinositide-3-kinase (PI3K) signaling pathway in human cancer is known and binding of EGCG with PI3K as a competitive inhibitor and competing ATP binding for metastatic control of cancer is a good support for EGCG as an anticancer agent (Van Aller et al. 2011).

For mechanistic reasons, biochemical pathways such as gene expression, growth factor-mediated pathway, mitogen-activated protein kinase-dependent pathway, and the ubiquitin/proteasome degradation pathways have been investigated to explore role of EGCG in cancer control (Chen et al. 2011). The ubiquitin-dependent degradation is important in the up-regulation of cell proliferation and down-regulation of cancer cell inhibition. Therefore, proteasome inhibitors, such as flavonoid chrysin, are important anticancer drugs, and targeting proteasomes is the appropriate strategy for cancer treatment (Sun et al. 2011). Proteasome inhibitors and other anti-angiogenesis inhibitors from several sources, such as marine, phytochemicals such as flavonoids (phenoxodiol) and metal complexes for use in anticancer therapy, have been investigated in detail (Frezza et al. 2011; Howes et al. 2011).

It is known that pro-apoptotic proteins are accumulated leading to cell death. The gap junction intercellular communication (GJIC) tumor suppressor, connexin (Cx), along with EGCG, play an important role in targeting human metastatic cancer cells (Choung et al. 2011).

The mechanism of apoptotic cell death is believed to be through down-regulation and/or suppression of cell death-inhibiting gene Bcl-xL (Sonoda et al. 2014). A down-regulation of ku70 by interrupting its binding with Bax mRNA and drug-metabolizing enzymes such as cytochrome P450 and peroxidoredoxin-V has been suggested as possible mechanism of action for cancer treatment (Li et al. 2013; Maliakal et al. 2011; Ren et al. 2011). EGCG also inhibits specific proteins with significantly altered expression level and signaling pathways such as EGFR and cell cycle in G0/ G1 phase arrest with an increase in G2M phase (Ma et al. 2014). This decreases the number of cells in ‘S’ phase consequently suppressing tumor-promoting effect of human peptidyl prolyl cis/trans isomerase (Urusova et al. 2011).

The altered proteins are known to be involved in drug resistance, gene expression, motility, detoxification, and metabolism in cancer cells. An inhibition of different cell lines offering different pathways indicates that EGCG and related compounds affect multiple pathways or global networks in cancer therapy by making topoisomerase–DNA complexes (Lopez-Lazaro et al. 2011).

Cytotoxicity of EGCG for colon cancer is known, due to its inhibition of DNA methyltransferases and histone deacetylases. While in human gastric cancer, EGCG controls recepteur d’origine nantais (RON) expression and it exerts its antineoplastic effects by antagonizing tumor-induced myeloid-derived suppressor cells (Park et al. 2013). The cytotoxic activity of EGCG is greatly enhanced when used as nano-gold particles (EGCG-pNG), and its mechanism of activity is shown to be through mitochondrial pathway-mediated apoptosis (Chen et al. 2014b).

Several other mechanisms of action of EGCG and theaflavin (TF3) in black tea extract have been proposed for their cytotoxicity including extracellular signaling, such as inhibition of Akt, NF-kappaB signaling by blocking phosphorylation and down-regulation of cyclooxygenase2, STAT3 signaling, down-regulation of TLR4 signal transduction, activation of 67-kDa laminin receptor (67LR), redox regulation, and genetic and epigenetic profile of tumor cells (Yiannakopoulou, 2014; Wang et al. 2013; Hong et al. 2010). The tumor-associated cell surface ubiquinone oxidase (ENOX2) is a cellular target for cancer inhibition by EGCG and isoflavone, phenoxodiol. Human carbonyl reductase 1(CBR1) is down regulated by EGCG thus potentiating the effect of antitumor drug anthracycline daunorubicin (DNR), by protecting it from reduction to its alcohol form (Huang et al. 2010).

Therefore, a combination of EGCG and DNR has been recommended for the treatment of hepatocellular carcinoma. A combination of TF3 with ascorbic acid (AA) or and EGCG plus AA is shown to enhance anticancer activities of catechins, such as EGCG, especially in breast cancer (Li et al. 2010).

The polypeptides (OATPs) 1B1 and 1B3 that assist organic anion transport are commonly produced in
follows. EGCG inhibits the amyloid plaque formation protective mechanism in AD may be categorized as decline in AD (Kuriyama et al. 2006). EGCG’s neuroactivity has been found to be a significant risk reducer for cognitive deposition (Ho et al. 2005). Green tea consumption has been related to amyloidosis (Betzaida et al. 2013). AD is characteristically marked by cognitive decline and etiologically related to amyloid deposition (Ho et al. 2005). Green tea consumption has been found to be a significant risk reducer for cognitive decline in AD (Kuriyama et al. 2006). EGCG’s neuroprotective mechanism in AD may be categorized as follows. EGCG inhibits the amyloid plaque formation (Bastienetto et al. 2006) and its toxicity through multiple pathways. Interference with the amyloid protein assembly and disruption/inhibition of fibril aggregation of amyloid plaques have been postulated (Ferreira et al. 2011). This destabilizes the amyloid plaque in the pipe line by altering the optimal binding of metals like Cu, needed for stability, leading to an alteration of amyloid fibril shape diminishing its neurotoxicity. Other neuroprotective and/or neuromodulator actions of EGCG may include protection against hydrogen peroxide-induced toxicity (Okello et al. 2011) and mitochondrial protection from amyloid toxicity (Dragicevic et al. 2011). It also ameliorates the amyloid toxicity on N-methyl-D-aspartate (NMDA) receptor function in brain cells. Aggregation of amyloid beta-protein stimulates the production of reactive oxygen species (ROS) through mitochondrial dysfunction, in neurons through NMDA-dependent pathway. This increase in ROS is quenched by EGCG helping AD suffering patients (He et al. 2011). It influences cell survival through down-regulation of pro-apoptotic genes (He et al. 2011) and promotes neural progenitor cell proliferation (Levites et al. 2002a). Green tea extract has also been shown to enhance the neuronal activity in the prefrontal cortical areas of brain concerned with processing of working memory (Borgwardt et al. 2012).

Oxidative stress and associated ROS generation, contributing to inflammation, may be implicated as one of the pathways in neurodegenerative diseases (Halliwell 2001). Both AD and PD pathology may show oxidative damage and increased iron accumulation in certain specific areas of brain (Reiderer et al. 1989). Similarities in pathology in AD and PD may include oxidative stress, increased lipid peroxidation, reduced mitochondrial activity, increased iron concentration, α-synuclein aggregation leading to neuronal toxicity, mitochondrial and cytochrome c oxidase malfunction (Recchia et al. 2004; Perry et al. 2002).

Tea drinking is associated with a moderate risk reduction for PD (Checkoway et al. 2002). Population studies including wide geographic areas have indicated a lower prevalence of PD in areas where tea drinking is more common (Zhang and Roman 1993). Neuronal protection by green tea extract has been demonstrated by experimental studies as well. Both EGCG and green tea extract have shown dopaminergic neuronal protection and prevention of striatal dopamine depletion against PD symptom complex inducing neurotoxin (Levites et al. 2001). Catechol amines in general are metabolized by COMT and MAO (Deleu et al. 2002). COMT inhibitors are often used in the clinical management of PD to improve bioavailability of levodopa in the brain (Bonifati and Meco 1999). Experimental, in vitro studies have revealed that EGCG has an inhibitory effect on COMT activity (Lu et al. 2003). However, more recent in vivo studies using high doses of EGCG did not show any impairment of COMT activity (Lorenz et al. 2014). The role of metal accumulation, like iron, copper, etc., related to oxidative stress in neurodegenerative diseases, is well established (Jomova et al. 2010). EGCG has shown possible neuroprotective property as an iron chelator (Temlett et al. 1994).

Further, role of oxidative stress in PD has been experimentally demonstrated using Paraquat, a powerful REDOX agent and especially toxic to nigrostriatal dopaminergic system (Liou et al. 2001). EGCG has shown a protective effect by inhibiting or attenuating peroxidation (Higuchi et al. 2003), cytotoxic cytokine release (McGeer and McGeer 1995), binding inhibition, and nuclear translocation of NF-κB or its down-regulation (Levites et al. 2002b). Neuronal protective effects of EGCG also include their ability to increase the activity of two major antioxidant enzymes, super oxide dismutase and catalase in the neostriatum of experimental animals (Chen et al. 2000), their ability to alter cell signaling pathways, and decrease or diminish pre-apoptotic gene expression (Weinreb et al. 2003).

Tea has anti-Alzheimer and anti-Parkinsonism activity

Neurodegenerative diseases like Alzheimer’s disease (AD) and Parkinson’s disease (PD) are among the front runners as a cause of mortality in the United States (Betzaida et al. 2013). AD is characterized by oxidative stress in PD has been experimentally demonstrated using Paraquat, a powerful REDOX agent and especially toxic to nigrostriatal dopaminergic system (Liou et al. 2001). EGCG has shown a protective effect by inhibiting or attenuating peroxidation (Higuchi et al. 2003), cytotoxic cytokine release (McGeer and McGeer 1995), binding inhibition, and nuclear translocation of NF-κB or its down-regulation (Levites et al. 2002b). Neuronal protective effects of EGCG also include their ability to increase the activity of two major antioxidant enzymes, super oxide dismutase and catalase in the neostriatum of experimental animals (Chen et al. 2000), their ability to alter cell signaling pathways, and decrease or diminish pre-apoptotic gene expression (Weinreb et al. 2003).
Green tea is anti-fibrotic

In this section, the results obtained in our laboratories are described. Green tea extract therapy detracts hepatic fibrosis induced by a combined exposure to carbon tetrachloride and ethanol, as shown by our histopathological studies (Safer et al. 2012). Hepatic fibrosis is a condition in which scar formation occurs in the liver. The process occurs during an excessive formation of extracellular collagenous matrix (ECM) (Bataller and Brenner 2005), or during a scar formation to replace normal tissue lost through injury, infection, or chronic liver insult. Specifically, hepatic fibrosis is a result of the inhibition of synthesis and degradation of the matrix due to insult occurring in the mesenchymal cells (MSCs) involved in the synthesis of various components of the ECM, including collagen types I–VII (Paz and Shoenfeld 2010). Results from our laboratories show that green tea extract (GTE) plays a beneficial role in controlling the fibrotic effects of reserpine (Al-Bloushi et al. 2009). Our results also show that the effect of hepatic fibrosis inducers such as carbon tetrachloride (CCl₄) and ethanol may also be avoided by GTE.

Inflammation often results in hepatic stellate cellular over-activity and this activity triggers ECM synthesis and a deposition of collagen fibers in the extracellular spaces of the liver cells. In this process, blood infusion is lost and the tissue hardens, leading to liver fibrosis (Wu and Zern 2000). Currently, there is no effective treatment for hepatic fibrosis, and a number of patients develop a progressive form of hepatic cirrhosis. We administered GTE to control the hepatic fibrosis-induced animal model. Hepatic fibrosis was induced by 4 weeks of CCl₄ aqueous solution administration to rats followed by GTE treatment, and we...
observed a decrease in the rate of damage to collagen fibers. Ethanol is also a hepatotoxin with a significant effect on the liver causing hepatic fibrosis (Yasuda et al. 2009). We investigated the therapeutic effect of GTE on the combined exposure to CCl₄ and ethanol, and results were analyzed with three-dimensional (3D) scanning electron microscopy. The data collected showed a progressive hepatic recovery from cirrhosis (Fig. 2). Analysis of our data shows that GTE chitosan nanoparticles are more effective in removing all the extracellular collagen fibers induced by CCl₄ in hepatic fibrosis.

From the nano-GTE perspective, it is obvious that it is very effective in healing and curing hepatic fibrosis with virtually no trace of fibers in the ECM (Safer et al. 2015).

### Nano-green tea and hepatic fibrosis

Nano-green tea, as chitosan encapsulated particles, has been recently used as an efficient method to control hepatofibrosis. We assessed this by Atomic Force Microscopy (AFM) in rat hepatic fibrosis model (Safer et al. 2015). AFM images revealed an abundance of collagen fibers of 250–300-nm width in the fibrotic liver samples while those of green tea chitosan nanoparticles (GTE-CS NPs) were clear of these fibers and were comparable with the control group (Fig. 3).

In our studies, healing effect quantification in hepatic fibrosis induced by GTE-CS NPs in rat model was carried out by analyzing data obtained by transmission (TEM) and

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**Fig. 4** Computational Image Analysis of the images of the ultra-thin section of the livers of rats from the four groups. Selected area with damaged cytoplasm and cytoplasmic organelles are colored in red. a Control cells, with normal architecture of hepatocytes (no damage). b, c, d are images with cells treated with CCl4/Ethanol, CCl4/Ethanol and nano-GTE and CCl4/Ethanol chitosan, respectively. The red colored area represents the selection of the damaged cytoplasm and cytoplasmic organelles in the cells (threshold). Note that the simple visual comparison of image c clearly indicates the significant healing of cytoplasm and cytoplasmic organelles. d representing group when compared to c very minor healing process. Pie charts and histograms below are the pictorial representation of the percentage damage (in red) and the undamaged regions (in gray) of adjacent cells belonging to the same groups.
scanning electron microscopy (SEM). A fixed volume of ~150 nm-sized chitosan-encapsulated GTE1 solution was orally administered to a group of adult rats for 3 weeks, after an individual treatment with CCl4 and ethanol for identical periods of time. Images of ultra thin sections of the liver samples were recorded using TEM (Fig. 4). Using computational analysis, the images were quantitatively probed revealing that chitosan nano-GTE healed nearly 25% of the sub-cellular area infected with hepatic fibrosis suggesting a significant therapeutic value of Chitosan nano-green tea extract. SEM study showed the topographical changes of cell surface as well as the extracellular matrix network between the hepatocytes.

Measurement and comparative analyses of data were carried out with various sets of TEM images of control healthy hepatic cells with undamaged cell cytoplasm. The results were supported by the SEM images. The architecture of the healthy tissue showed some uneven, rough, and discrete 'pebble'-like surface, with some irregular invaginated portions seen as black regions. However, surface of the damaged cells appeared as perforated and meshed and had lost integrity as compared with the control tissues. Contrarily, treatment with nano-green tea clearly showed significant improvement, eliminating perforation, meshy regions, and the formation of 'pebble'-like structures with good resemblance to the healthy tissue.

A computational analysis of the TEM images showed marked differences in the percentage of the damaged area in the hepatic cells among the different groups of rats. The worst damage was with the dual effect of CCl4 and ethanol, followed by the effect of CCl4+ ethanol and chitosan nano-GTE. A substantial improvement was detected in the group of rats, which was exposed to CCl4+ ethanol and chitosan nano-GTE.

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Conflict of interest The authors declare no conflict of interest.

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inhibits both the metastasis and osteolytic components of mammary cancer 4T1 lesions in mice. J Nutr Biochem 25(4):395–403


