PharmacologyOnLine

Archives • 2021 • vol.3 • 1156-1166

NUTRACEUTICAL FUNCTIONS OF GREEN TEA

Bonomo, Maria Grazia[1,7]; Catalano, Alessia[2]; Finelli, Francesca[3,*]; Giuzio, Federica[4]; Iacopetta, Domenico[5]; Ceramella, Jessica[5]; Sinicropi, Maria Stefania[5]; Capasso, Anna[6]; Saturnino, Carmela[1]

[1]*University of Basilicata, Department of Science, Viale dell'Ateneo Lucano n. 10, 85100 Potenza, Italy*
[2]*University of Bari "Aldo Moro", Department of Pharmacy-Drug Sciences, Via Orabona n. 4, 70126 Bari, Italy*
[3]*Struttura Complessa UOP-AO "G. Moscati" Avellino, Italy*
[4]*International PhD Programme 'Sciences', University of Basilicata, Department of Science, Viale dell'Ateneo Lucano n. 10, 85100 Potenza, Italy*
[5]*University of Calabria, Department of Pharmacy, Health and Nutritional Sciences, 87036 Arcavacata di Rende, Italy*
[6]*University of Salerno, Department of Pharmacy, Via Giovanni Paolo II n. 132, 84084 Fisciano (SA), Italy*
[7]*Spinoff TNcKILLERS, Viale Dell'Ateneo Lucano 10, 85100 Potenza, Italy*

**medfinelli@gmail.com*

Abstract

Today, the diffusion of neoplastic diseases is a widespread phenomenon. Thus, it is always necessary to identify new molecules able to fight them. In this paper, we will deal with the interesting antineoplastic properties of green tea. We will describe the different and plausible anticancer mechanisms of epigallocatechin gallate (EGCG), the major polyphenol found in green tea, and in particular the biochemical and computational discovery of a new target for the treatment of this disease will be discussed. The bio-active substances present in tea are essentially represented by methylxanthines, as well as by the antioxidant phenolic fraction (flavonoids). Among the other active substances contained in lower concentrations there are vitamins (B, C and K), amino acids (L-theanine) and minerals (aluminium and manganese). Tea extracts, particularly EGCG, could represent the starting point for the potential emergence of new drugs for the treatment of neoplastic diseases. Other activities of tea, as the involvement in neurodegenerative diseases prevention, as well as the antioxidant, antibacterial, antifungal and antiviral effects, will be also briefly described.

Keywords: *tea, epigallocatechin gallate (EGCG), tumor, flavonoids, green tea catechins (GTCs), nutraceuticals.*

Introduction

Tea is the most consumed drink in the world after water. Green tea is a non-fermented tea that contains numerous components endowed with antioxidant activity, including phenols (especially catechins) [1]. Phenols constitute an important class of secondary metabolites mainly widespread in the plant kingdom. They are responsible for many organoleptic characteristics appearing both as precursors of aromas and colours, and for their nutritional characteristics [2,3]. Tannins are phenols known for their activity as astringents, anthocyanins for the colours of the flowers, phenolic acids for the acidic taste, and some flavonoids for the bitter taste. The total phenolic compounds can reach 35% of the composition of the dry tea leaves. Fermentation modifies the qualitative and quantitative composition of the tea phenols giving rise to complex polyphenols represented by aromatic and coloured compounds such as tea flavins and tea rubigo (flavonols) present mainly in black tea. In green and yellow teas, oxidation is deliberately blocked by inhibiting the action of oxidase. Therefore, during the growth of the leaves on the plant, the content of polyphenols decreases quantitatively and qualitatively: thus, the best quality of tea is obtained from young leaves [4]. Phenols are responsible for the numerous beneficial activities of green tea. Polyphenols are proposed to function via various mechanisms, the most important of which is related to reactive oxygen species (ROS) [5,6]. Moreover, noticeable melatonin contents were found in green tea [7-9]. The bioactive components of green tea, especially polyphenols, showed antioxidant capacity and inhibitory effects against digestive enzymes that will be briefly described in this paper.

Flavonoids

Flavonoids are among the most abundant phenolic compounds present in green tea [10-14]. Their structure consists of a diphenylpropane skeleton, *i.e.* two benzene rings connected by a closed pyranic ring. The innumerable structural characteristics of the ring and the glycosylation and dihydroxylation patterns of the three rings, make the flavonoids the largest group of natural molecules with multiple biological activities, such as antioxidant, anti-inflammatory, antihypertensive and antiviral [15-20]. Flavonoids can be classified into several classes: flavones, flavonols, flavanones, flavanonols, flavanols or catechins and anthocyanins [21]. They have been recently studied for new pharmaceutical preparations, such as nanoformulations and incorporation into liposomes, in order to improve their bioavailability [22-28]. Among them, our attention was focused on flavanols (catechins), which are a sub group of flavonoids and represent about 20-30% of the total weight. The main catechins in tea, named green tea catechins (GTCs) are: epigallocatechin-3-gallate (EGCG), mainly responsible for the beneficial effects of tea, epigallocatechin (EGC), epicatechin-3-gallate (ECG) and epicatechin (EC) (Figures 1-4).

EGCG

The benefits of green tea correspond for the most part to the benefits of the catechins it contains, namely EGCG. The main activity of EGCG is to enhance the antioxidant defences and therefore decrease cell damage, producing healthy effects on all tissues. Green tea has 10 times higher EGCG content than black tea (about 180 mg per cup of green tea) and 2.5 times higher than oolong tea. EGCG is among the most studied and most abundant catechins in tea, accounting for 50-80% of the total catechin content [29,30]. The nutritional health properties of EGCG may be related to its structure, with three aromatic rings linked together by a pyranic ring. The antioxidant activity of EGCG results from the transfer reactions of a hydrogen atom or a single electron, involving the hydroxyl groups of the rings [31]. The onset and progression of cancer are linked to epigenetic alterations including aberrant methylation and acetylation of DNA. EGCG is, therefore, a molecule capable of inhibiting tumors, particularly of the lung, oral-digestive tract, and prostate. An association between green tea consumption and reduced risk of stomach cancer was demonstrated in Japan [32]. One of the most promising studies in prostate cancer was performed by Bettuzzi et al. [33], who demonstrated that GTCs are safe and very effective for treating premalignant lesions before prostate cancer develops. Two hundred individuals with high-

grade prostatic intraepithelial neoplasia received 600 mg of GTCs or placebo for 12 months. EGCG in mice was shown to inhibit lung carcinogenesis induced by a specific nitrosamine of tobacco, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, by inhibiting the formation of 8 hydroxy-deoxyguanosine [34]. Moreover, daily consumption of green tea, and diets rich in natural polyphenols have been linked to a reduced risk of inflammatory bowel disease (IBD) [35,36].

EGCG activities

Inhibition of angiogenesis

Tumor growth is closely related to angiogenesis, which supplies oxygen and nutrients to cancer cells [37,38]. Vascular endothelial growth factor (VEGF) has been recognized as one of the main angiogenic factors. EGCG was shown to inhibit angiogenesis and tumor growth, by down-regulating VEGF expression in HT29 human colon cancer cells, cultured in the absence of serum and in vivo, as well as in human breast cancer and pancreatic cancer cells [10,39]. In addition to this activity, EGCG also modulates the activity of epidermal growth factor receptor (EGFR) and platelet growth factor receptor (PDGFR), tyrosine kinase proteins implicated as contributing factors in the proliferation of cells. The mechanisms responsible for modulation of the EGFR signal are different: the inhibition of EGFR autophosphorylation [40]; the increase in EGFR phosphorylation on Ser1046/1047 by the mitogen-activated protein kinase p38 (MAPK) in colon cancer, resulting in down-regulation of EGFR expression [41]; the induction of the internalization of EGFR in the endosome [42]; the modulation of membrane lipid organization, and therefore the inhibition of binding of EGF to EGFR [43]. Furthermore, EGCG also inhibits PDGFR phosphorylation, its downstream signalling in smooth muscle cells and spheroidal formation of human gliobastoma cells [44].

Inhibition of tumor migration

The inhibition of migration and invasion of tumor cells could also be a target of antineoplastic therapy. EGCG downregulates hepatocyte growth factor (HGF)-induced matrix metalloproteinases, particularly MMP-9 and determines the activation of urokinase-type plasminogen activator (uPA) capable of inhibiting invasion and metastasis in hypopharyngeal carcinoma cells [45].

Induction of cell death

Apoptosis is a key strategy that is responsible for deletion of cells in normal tissues; it also occurs in specific pathologic contexts. The relationship between antiapoptotic (Bcl-2 and Bcl-xL) and proapoptotic (Bax and Bak) factors of the Bcl-2 family, decides cell susceptibility against anti-drugs tumors in cancer cells. Furthermore, apoptotic proteins with only one BH domain (BH3-only including PUMA, Noxa, and Bim) bind with Anti-Bcl-2 proteins to inhibit their functions, resulting in the induction of apoptosis. Several studies have reported that EGCG modulates the expression of the Bcl-2 family of proteins: it induces apoptosis by down-regulation of Bcl-2 and/or up-regulation of Bax expression in nasopharyngeal carcinoma cells, breast, prostate, bladder and ovarian. On the other hand, the induction of PUMA by EGCG also leads to apoptosis in colon cancer cells. The modulation of the expression of the Bcl-2 family of proteins by EGCG is one of the important factors for the induction of cell death by apoptosis: in this case, the tumor suppressor genep53 plays a critical role in the inhibition of carcinogenesis through cell cycle regulation, apoptosis and DNA repair. Therefore, p53-mediated signalling is involved in anticancer drug apoptosis. EGCG may be able to induce p53-mediated cell death by inducing the activity and stabilization of this molecule. In prostate and breast cancer cells, EGCG increases the expression of Bax, a downstream target of p53 [46,47].

EGCG targets

Inhibition of kinases

In recent years, multi-target kinase inhibitors have become a focal point of interest for physicians, pharmacists and medicinal chemistry researchers. Some of them have been recently approved in antineoplastic therapy [48-50]. Therefore, the broad inhibition of multiple targets, rather than a single

specific target, could represent a more comprehensive strategy for the treatment of malignancies and other diseases [51-57]. Studies *in vitro* demonstrated that EGCG was able to inhibit the proliferative mechanism of some tyrosine kinases (RTKs) including EGFR, IGF-1REVEGFR, by inhibiting the phosphorylation of these receptors. The block of MAPK and PI3K signalling pathways results in the downstream inactivation of the transcription factors AP-1 and NfKB, whose cell proliferative activity is unregulated in subjects affected by neoplasia. The anticarcinogenic activity of EGCG has in fact been confirmed recently thanks to the computational discovery of a new target: it is a serine–threonine kinase (RSK2), another factor implicated in cell proliferation [58]. The computational screening of the molecules able to bind it specifically, only anticipated what was then identified in vitro: EGCG binds the RSK kinase on both N and T terminal catalytic domains, preventing phosphorylation and therefore the activation of both the protein, same as its substrate; all this, therefore, leads us to reflect on a better activity of catechin towards multiple targets.

Inhibition of histone H3 phosphorylation

The 90 kDa ribosomal S6 kinase-2 (RSK2) is a growth factor-stimulated protein kinase. It translocates to the nucleus when activated by growth factors, peptide hormones, or neurotransmitters: once in the nucleus, RSK2 can phosphorylate various nuclear proteins, including several histones, thus mediating numerous cellular processes [59]. One of its known phosphorylation substrates is histone H3 [60,61]. EGCG was shown to influence the ability of RSK2 to phosphorylate histoneH3 through a kinase immune-precipitation assay. The complete structure of RSK2 was transfected into 293 cells and subsequently the RSK2 proteins were immune precipitated with specific antibodies. The precipitates were directly subjected to an *in vitro* kinase test with histone H3 (1µg) as substrate. The following treatment with EGCG resulted in a dose-dependent inhibition of Ser10 phosphorylation of histone H3 [58]. Based on its broad substrate specificity, the RSK2 protein could mediate a variety of cellular processes, such as cellular proliferation and transformation. RSK2 was demonstrated to play an important role in cell transformation induced by tumor promoters such as EGF and TPA [62]. Overall, these results indicate that EGCG is a novel natural compound that effectively inhibits RSK2 activity. Furthermore, the results showed that EGCG has a high similarity to two known RSK2 inhibitors, quercitrin [63] and afzelin [64], a further valid element for a better understanding of the chemopreventive activity of this molecule.

Antibacterial, antifungal and antiviral effects of green tea

Over the past two decades, several studies have reported that EGCG has anti-infective properties. Its antiviral activity has been demonstrated towards several families of viruses, such as Retroviridae, Orthomyxoviridae and Flaviviridae which include important human pathogens such as virus (HIV), influenza A virus and hepatitis C virus [65]. Furthermore, EGCG seems to interfere with the DNA replication cycle of viruses such as that of hepatitis B, the herpes simplex virus and adenovirus [66]. The use of green tea is used for the treatment of oral potentially malignant disorders (OPMDs), such as lichen planus [67], along with pharmacological therapies, such as thalidomide [68]. Recently, its potential application in coronavirus disease 2019 (COVID-19) has been proposed [69,70]. However, even if the molecular effects of EGCG have not been fully understood yet, there are results that indicate that it binds to lipid membranes and affects the folic acid metabolism of bacteria and fungi by inhibiting the cytoplasmic dihydrofolatoreductase enzyme: this mechanism would explain the antibacterial, antifungal and antiviral effects of EGCG [71]. EGCG was recently shown to act against biofilms, ubiquitous multicellular aggregates of bacteria or fungi generally refractory to antibiotic treatment [72]. Biofilm formation was demonstrated to be impaired by EGCG for many more bacteria, also difficult to eradicate, such as *Enterococcus faecalis* [73,74] and *Candida* spp. [75].

Effect of green tea in neurodegenerative diseases and antioxidant activity

Green tea prevents neurodegenerative diseases. *In vitro* studies demonstrate the protective effects

of GTCs in neurodegenerative diseases: some neuroprotective studies have shown that both green tea extract and EGCG have very potent activity in preventing striatal dopamine (DA) depletion and grey matter in the central nervous system loss in dopaminergic neurons of mice. Furthermore, the same researchers reported EGCG ability to chelate iron. This finding gives further hope for its neuroprotective effect as iron accumulates in neurons and microglia of the nervous system of patients with Parkinson's [76]. Green tea has been recently shown to reduce oxidative stress in part by its ability to bind free iron, a micronutrient that is both essential for and toxic to all living organisms. Green tea may act to increase the lifespan of the fruitfly *Drosophila melanogaster* in part by the regulation of iron regulators, specifically, *mitoferrin*, a mitochondrial iron transporter, and reduction of mitochondrial iron [77-79].

Conclusions

The habitual consumption of tea could be an effective method for the prevention of certain diseases over time. The study of the effects of tea at the molecular level, leading to the isolation of active substances, seems to improve the conditions of several diseases. However, it is too early to state with certainty the therapeutic activity of green tea extracts in the treatment of the diseases. Surely, *in vitro* studies have shown that EGCG, the main polyphenolic component of green tea, is an efficient substance for various molecular targets. Unlike specific inhibitors of single targets, EGCG is as an inhibitor of multiple signalling pathways. It might be able to reduce drug resistance by hindering the activation of alternative signalling pathways, thus representing the first step towards the introduction of a new drug, able to act against many and important diseases such as cancer.

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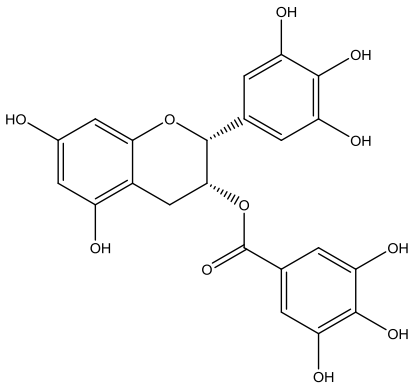

Figure 1. Structure of epigallocatechin-3-gallate (EGCG).

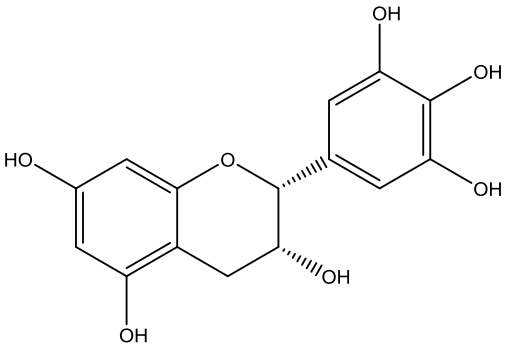

Figure 2. Structure of epigallocatechin (EGC).

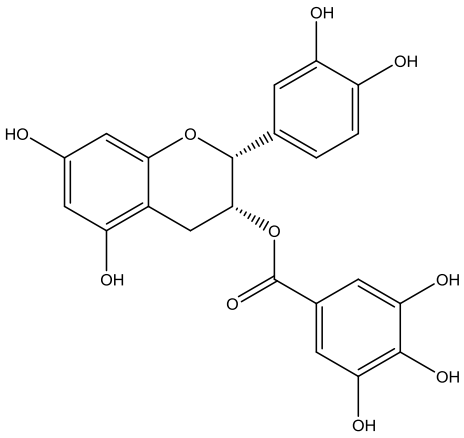

Figure 3. Structure of epicatechin-3-gallate (ECG)

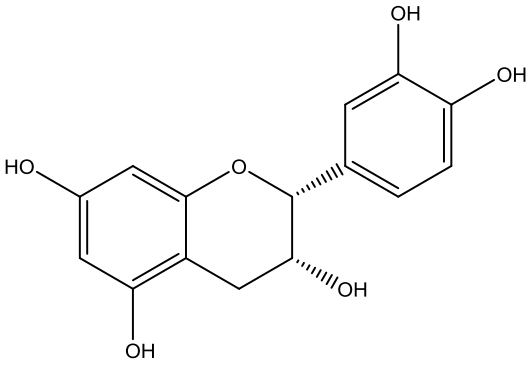

Figure 4. Structure of epicatechin (EC).