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Review

Epigallocatechin gallate and mitochondria—A story of life and death

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ABSTRACT

Epigallocatechin gallate (EGCG) is a flavonoid belonging to the chemical class of falvan-3-ols (catechins) esterified with gallic acid. It is the main catechin found in green tea (*Camellia sinensis* L.) accounting for about 50% of its total polyphenols. Extensive research performed in recent years has revealed that green tea demonstrates a wide range of positive biological activities against serious chronic diseases such as cardiovascular and neurodegenerative pathologies, cancer, metabolic syndrome and type 2 diabetes. These protective properties can be traced back to the potent antioxidant and anti-inflammatory activities of EGCG. Recent studies have suggested that it may exert its beneficial effects by modulating mitochondrial functions impacting mitochondrial biogenesis, bioenergetic control (ATP production and anabolism), alteration of the cell cycle, and mitochondria-related apoptosis. This review evaluates recent evidence on the ability of EGCG to exert critical influence on the above mentioned pathways.

Contents

Abbreviations: ADP, adenosine diphosphate; AIF, apoptosis-inducing factor; ALT, alanine aminotransferase; AMP, adenosine monophosphate; AP-1, activator protein-1; ASK1, apoptosis signal-regulating kinase 1; ATP, adenosine triphosphate; Bax, BCL2-Associated X Protein; Bcl-x_L, BCL2-like 1 isoform 1; Bcl2, B-Cell CLL/Lymphoma 2; Bid, BH3-interacting domain death agonist; CAMP, cyclic AMP; CAT, catalase; CGN, cerebellar granule neuron; COMT, catechol-*O*-methyltransferase; CREB, cAMP response element-binding protein; CS, citrate synthase; CsA, cyclosporin A; DRP1, dynamin-related protein 1; DS, Down's syndrome; DYRK1A, dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A; EGCG, epigallocatechin gallate; EGFR, epidermal growth factor receptor; EndoG, endonuclease G; ER, endoplasmic reticulum; ERK, extracellular signal-regulated kinase; FasL, tumor necrosis factor ligand superfamily member 6; γ-GCL, γ-glutamatecystein ligase; GCLC, glutamate—cystein ligase catalytic subunit; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GSK3β-, glycogen synthase kinase-3β; GSSG, oxidized glutathione; GST, glutathione S-transferase; HER2, human epidermal growth factor receptor-2; HO-1, heme oxygenase-1; IDH, isocitrate dehydrogenase; IFN-γ, interferon-γ; IL-1β, interleukin-1β; IL-6, interleukin-6; INDO, indomethacin; iNOS, NO synthase; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; KDH, α-ketoglutarate dehydrogenase; L-DOPA, levodopa; MAO-A, monoamine oxidase-A; MDH, malate dehydrogenase; METC, mitochondrial electron transfer chain; MKK, mitogen-activated protein kinase kinase; Mnf2, mitofusin 2; MMP, mitochondrial membrane potential; MPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; Nanog, Homeobox protein NANOG; NF-κB, nuclear factor-κB; NRF-1, nuclear respiratory factor 1; Nrf2, nuclear factor erythroid 2-related factor 2; Oct4, octamer-binding transcription factor 4; OPA1, optic atrophy 1 gene protein; PARP, poly [ADP-ribose] polymerase 1; PGC-1α, peroxisome proliferator-activated receptor γ co-activator-1α; PI3K, phosphoinositide-3-kinase; PKA, protein kinase A; PKB, protein kinase B; ROS, reactive oxygen species; SDH, succinate dehydrogenase; SIRT1, NAD^+-dependent protein deacetylase sirtuin-1; SOD, superoxide dismutase; Sox2, SRY (sex determining region Y)-Box 2; STAT3, signal transducer and activator of transcription 3; TCA, tricarboxylic acid cycle; TFAM, mitochondrial transcription factor A; TGF-β, transforming growth factor-β; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; VDAC1, voltage-dependent anion-selective channel protein 1; VEGF, vascular endothelial growth factor.

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1. Introduction

Mitochondria, named by Benda in 1898 [1], are double membrane-bound organelles first discovered and studied in the 1840s by several research groups worldwide [2]. The main role of the 10 million billion mitochondria throughout the human organism is oxidative phosphorylation, leading to the production of adenosine triphosphate (ATP) in almost all body cells. The mitochondrial electron transport system is a site for reactive oxygen species (ROS). The most reactive ROS are the superoxide radical anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($^{\bullet}OH$). ROS are partially eliminated from the mitochondria by antioxidant enzymes (such as superoxide dismutase, SOD1 and SOD2), and released into the cytosol where other antioxidant enzymes (*i.e.*, glutathione peroxidases, catalase, and peroxiredoxins) perform their function. Therefore, mitochondrial and cellular antioxidant enzymes are essential for the maintenance of normal mitochondrial function, especially in highly oxidative tissues such as brain, heart and liver. In fact, the overproduction of ROS and deficiency of antioxidant enzymes leads to oxidative stress, in which ROS (due to their high reactivity) directly oxidize proteins, unsaturated fatty acids, and DNA, inducing mitochondrial dysfunction and cell damage [3].

Human mitochondria host about 1500 different types of proteins, but only about 13 of them are coded by the mitochondrial DNA (mtDNA). This means that most of the human mitochondrial proteins are nuclear encoded, synthesized in the cytosol, and targeted to mitochondria [4,5].

About 3% of mitochondrial proteins code for ATP production proteins, while the other proteins are involved in processes different from ATP production, indicating that the other mitochondrial proteins are involved in processes different from ATP synthesis. Recently a comprehensive database of human mitoproteome was developed (www.mitoproteome.com) [6].

Due to the complexity of mitochondrial structure and metabolism, the simplistic concept of mitochondria as ATP producers in response to energy demand has been overridden in recent decades by the discovery that these organelles are involved in a wide array of metabolic and signaling processes, central to the cell cycle (life, death and differentiation). In particular, mitochondria were discovered to play a central role in the process of programmed cell death. The role of cytochrome c, an electron carrier in the oxidative phosphorylation system, was found at the end of the 1990s. Upon apoptotic insult, cytochrome c is released from the mitochondria, whereupon it initiates caspase activation and the execution of apoptosis [7]. This discovery paved the way to new findings that contribute to our current understanding of mitochondrial cell death pathways. Subsequent investigations performed in the 1990s and early 2000s lead to the discovery of the role of mitochondrial dysfunction in many rare and common human diseases and in the aging process [8–10]. Today, in fact, it is well known that mitochondrial dysfunction is observed in more than 50 inborn metabolic errors, as well as metabolic disorders (*e.g.*, metabolic syndrome, type 2 diabetes), neurodegenerative diseases (*e.g.*, Parkinson's disease and Alzheimer's diseases), and also some forms of cancer.

Epigallocatechin gallate (EGCG) is a flavonoid belonging to the chemical class of falvan-3-ols (catechins) esterified with gallic acid. While catechins are found in a variety of vegetable foods and beverages such as fruits, chocolate, wine and tea, EGCG is the main catechin found in green tea (*Camellia sinensis* L.), accounting for more than 50% of total green tea polyphenols. Epidemiological studies carried out to evaluate the effect of green tea consumption on human health, and the extensive research performed both on green tea and EGCG, revealed that this compound shows cardioprotection, neuroprotection, renal protection, osteoprotection, anticancer properties and the ability to manage obesity, metabolic syndrome and type 2 diabetes [11]. The link between oxidative stress and inflammation is well accepted and the health benefits of green tea and EGCG have been traced back to the antioxidant and anti-inflammatory activities of epigallocatechin gallate which increases the expression levels of antioxidant enzymes and inhibit the activation of Toll-like receptor 4 (TLR4) and nuclear factor-κB (NF-κB) pathways, leading to the increased production of inflammatory cytokines [12]. This paper aims to collect, critically analyze and summarize recent evidence on the effects of EGCG on mitochondrial function and dysfunction at the molecular level, with particular attention to the beneficial effects of modulating mitochondrial processes on mitochondrial biogenesis, bioenergetics control (ATP production and anabolism), alteration of cell cycle, mitochondrial membrane potential, and mitochondria-induced apoptosis. Therefore, this review aims to elucidate the molecular and cellular basis behind the protective effect of EGCG in the prevention of chronic diseases. Moreover, to give a complete picture of the potential of EGCG, its chemistry, safety, and bioavailability are also discussed.

2. Chemistry and isolation of EGCG

Catechins are polyphenolic flavanols ubiquitous in vascular plants and potentially beneficial to human health. Their basic structure is a diphenylpropane skeleton, with benzene A ring similar to a resorcinol moiety, an aromatic B ring related to a catechol moiety and a C ring which is a dihydropyran heterocycle unit with a hydroxyl group on carbon 3.

Catechins contain two asymmetric carbon atoms at C-**2** and C-**3**, giving them four diastereoisomers. Two of the isomers are in a *trans* configuration and are called catechin and the other two are in *cis* configuration and are called epicatechin. (+)-Catechin and (−)-epicatechin are found in fruit, but dark chocolate contains the highest catechin levels (459.8–610.0 mg/kg). Vegetables and legumes are poor dietary sources of catechins: only rhubarb, broad beans, and marrowfat peas contain catechins [13]. Catechins are also present as gallic acid conjugates, namely, (+)-gallocatechin, (−)-epigallocatechin, (−)-epicatechin gallate, and (−)-EGCG. These compounds are limited to a few products. EGCG, chemically (2R,3R)-2-(3,4,5-tryhydroxyphenyl)-3,4-dihydro-1 (2H)-benzopyran-3,5,7—triol 3-(3,4,5-trihydroxybenzoate), is the major catechin of green tea, occurring in concentrations ranging from 9 to 13% [14]. Many researchers suggest that EGCG is responsible for the majority