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Review

Molecular understanding of Epigallocatechin gallate (EGCG) in cardiovascular and metabolic diseases

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ABSTRACT

Ethnopharmacological relevance: The compound epigallocatechin-3-gallate (EGCG), the major polyphenolic compound present in green tea [*Camellia sinensis* (Theaceae], has shown numerous cardiovascular health promoting activity through modulating various pathways. However, molecular understanding of the cardiovascular protective role of EGCG has not been reported.

Aim of the review: This review aims to compile the preclinical and clinical studies that had been done on EGCG to investigate its protective effect on cardiovascular and metabolic diseases in order to provide a systematic guidance for future research.

Materials and methods: Research papers related to EGCG were obtained from the major scientific databases, for example, Science direct, PubMed, NCBI, Springer and Google scholar, from 1995 to 2017.

Results: EGCG was found to exhibit a wide range of therapeutic properties including anti-atherosclerosis, anti-cardiac hypertrophy, anti-myocardial infarction, anti-diabetes, anti-inflammatory and antioxidant. These therapeutic effects are mainly associated with the inhibition of LDL cholesterol (anti-atherosclerosis), inhibition of NF-κB (anti-cardiac hypertrophy), inhibition of MPO activity (anti-myocardial infarction), reduction in plasma glucose and glycated haemoglobin level (anti-diabetes), reduction of inflammatory markers (anti-inflammatory) and the inhibition of ROS generation (antioxidant).

List of abbreviations: AAC, abdominal aortic constriction; ACC, acetyl-CoA carboxylase; ADR, adenosine receptor; AE, alveolar epithelial; AF, atrial fibrillation; AGEs, advanced glycation end products; ALP, alkaline phosphatase; ALT, alanine transaminase; AMPK, AMP-activated protein kinase; Ang II, angiotensin II; ANP, atrial natriuretic polypeptide; AP-1, activator protein-1; aP2, adipocyte fatty acid-binding protein-2; AR, aldose reductase; AST, aspartate transaminase; ATGL, adipose triglyceride lipase; BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; BNP, brain natriuretic polypeptide; CABG, coronary artery bypass grafting; Cas, caspase; CC, corpus cavernosum; CCL2, chemokine C-C motif ligand 2; CD, cyclodextrins; CD44, cell-surface glycoprotein; C/EBT-α, CCAAT enhancer-binding protein-α; CKMB, creatine kinase; CL-HPLC, chemiluminescence detection-high performance liquid chromatography; COL1A1, α-1 type 1 collagen; COX-2, cyclooxygenase-2; CPK, creatine phosphokinase; CPT-1, carnitine palmitoyl transferase-1; CRP, C-reactive protein; CTGF, connective tissue growth factor; cTn, cardiac troponin; CVD, cardiovascular disease; DDC, diethyldithiocarbamate; DM, diabetes mellitus; DPPH, 1,1-diphenyl-β-picrylhydrazyl; DOX, doxorubicin; eEf2, eukaryotic elongation factor-2, EGCG, epigallocatechin gallate; ERK, extracellular regulated kinase; EWP, egg white protein; FAS, fatty acid synthase; FasR, Fas receptor; FFA, free fatty acid; FN, fibronectin; GCA, germ cell apoptosis; GK, glucokinase; GSH, glutathione; GSK, glycogen synthase kinase; GPX, glutathione peroxidase; GTE, green tea extract; H/R, hypoxia/reoxygenation; HbA1C, glycosylated haemoglobin; HDL, high density lipoprotein; HFD, high-fat diet; HNE, hydroxynonenal; HO-1, heme oxygenase-1; HOMA-IR, homeostasis model assessment for insulin resistance; HR, heart rate; HREC, human retinal epithelial cell; HSC, hepatic stellate cell; HSL, hormone sensitive lipase; HSP 60, heat shock protein 60; HUVEC, human umbilical vein endothelial cell; hyp, hydroxyproline; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; iNOS, inducible nitric oxide synthase; I/R, ischemia reperfusion injury; IRS-1, insulin receptor substrate-1; ISO, isoprenaline; JNK, c-Jun N-terminal kinase; LDH, lactate dehydrogenase; LDL, low density lipoprotein; LPA, lysophoaphatidic acid; LPL, lipoprotein lipase; LOX-1, lectin-type oxidized LDL receptor-1; LV, left ventricular; MAPK, mitogen-activated protein kinase; Mb, myoglobin; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; ME, malic enzyme; MGO, methylglyoxal; MI, myocardial infarction; MMP, matrix metallopeptidase; MnSOD, manganese superoxide dismutase; MPO, myeloperoxidase; NF-kB, nuclear factor kappa b; NOS-2, nitric oxide synthase-2; NOX-4, NADPH oxidase-4; Nppa, natriuretic peptidase type A; NQO-1, NADPH quinone oxidoreductase-1; Nrf-2, nuclear transcription factor NF-E2-related factor 2; NT, nitrotyrosine; 8-oxo-dG, 8-hydroxydeoxyguanosine; OPN, osteopontin; OPR, opioid receptor; p22phox, human neutrophil cytochrome b light chain; PARP, poly(ADP-ribose) polymerase; PCB, polychlorinated biphenyl; PD, peritoneal dialysis; PDGF, platelet-derived growth factor; PE, phenylephrine; PEPCK, phosphenolpyruvate carboxykinase; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; RQ, respiratory quotient; SAA, serum protein amyloid A; SCD-1, stearoyl-CoA desaturase-1; Sirt-1, NAD-dependent deacetylase sirtuin-1; SMA, smooth muscle actin expression; SREBP-1C, regulatory element-binding protein 1-C; STAT-1, signal transducer and activator of transcription-1; STZ, streptozotocin; SOD, superoxide dismutase; SULT, sulfotransferase; TAG, triacylglycerol; TC, total cholesterol; TG, triglyceride; TGF, transforming growth factor; TIMP, tissue inhibitor metallopeptidase; TLR, toll-like receptor; tMCAO, transient middle cerebral artery occlusion; TNF-α, tumor necrosis factor alpha; TnT, troponin T; TRF_2, telomere repeat-binding factor 2; TT, testicular torsion; UCP-2, uncoupling protein-2; UGT, UDP-glucuronosyltransferase; VEGF, vascular endothelial growth factor

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Conclusion: EGCG shows different biological activities and in this review, a compilation of how this bioactive molecule plays its role in treating cardiovascular and metabolic diseases was discussed.

1. Introduction

Cardiovascular disease (CVD), a kind of disease due to abnormal function of the heart as well as blood vessels, is known as the number one killer worldwide. It includes coronary heart disease, congenital heart disease, rheumatic heart disease, cerebrovascular disease and peripheral arterial disease. According to the 2013 Global Burden of Disease study, approximately 17.3 million deaths were caused by CVD, which represents 31.5% of all deaths. Among these, 7.4 million were having coronary heart disease and 6.7 million died due to stroke (European et al., 2016). Usually, a heart attack or stroke would be the first warning of underlying diseases. Both of them are acute events that are mainly caused by the presence of fatty deposits which block blood from flowing smoothly in the blood vessels and this event is known as atherosclerosis (Go et al., 2013; European et al., 2016). However, stroke can also be caused by the formation of blood clots. Framingham Heart Study found that the risk factors that lead to CVD through metabolic syndrome (diabetes and obesity) includes poor glucose tolerance, physical inactivity, tobacco use, hypertension, and high level of blood cholesterol (Go et al., 2013).

Numerous clinical approaches had been done to alleviate and cure CVD but none of were proven to show perfect results. Side effects including nausea and vomiting, dizziness, angina and edema are the typical symptoms when patients are given CVD medication therapies (Nagle et al., 2006). Transplantation of heart may be a hope for those patients who fail to recover from the conventional therapies, but there is a chance of organ rejection and the number of donors are limited. Hence, herbal medicine became another useful alternative therapy as they do not show any side effects. In addition, they are relatively cheaper than pharmaceutical drugs, easily acquired and can be used for multipurpose. One of the most valuable advantages of herbal medicine is that it helps in utilizing the body's natural healing process as it contains ingredients that are regularly produced by the body. Amongst numerous herbal medicines that have been discovered, green tea is found to be one of the therapeutic agents with most potential against CVD.

Green tea is the least processed tea from the buds of *Camellia sinensis* plant and it contains Epigallocatechin gallate (EGCG), which is an ester that forms from the reaction of epigallogatechin and gallic acid (Zaveri, 2006). EGCG can be found abundantly in green tea leaves (7.1 g per 100 g green tea leaves), oolong tea (3.4 g per 100 g oolong tea), and black tea leaves (1.1 g per 100 g black tea leaves) (Chacko et al., 2010). In Traditional Chinese Medicine and Ayurvedic practices, green tea has been used extensively as a stimulant, diuretic and astringent. Other traditional uses of green tea include promoting digestion, improving mental health and regulating blood sugar as well as body temperature (Cooper et al., 2005). Furthermore, due to the presence of catechin in EGCG, scientists believe that it may act as an antioxidant which plays a role in reducing the amount of free radicals involved in numerous diseases states including CVD (Lobo et al., 2010). This makes scientists believe that EGCG could be a potential therapeutic agent against CVD, which are mainly caused by oxidative stress. However, a review to understand the cardiovascular protective role of EGCG from molecular aspect has not been reported. This review aims to compile the information from preclinical (*invivo* and *invitro)* and clinical studies that had been done by collecting research journals published from the past 12 years (1995–2017) on this bioactive molecule.

2. Method

The information on EGCG (Fig. 1) relating to cardiac and metabolic diseases were collected from several databases such as Science direct, PubMed, NCBI, Springer and Google scholar, limiting publications from 1995 to 2017. We have searched the work related to EGCG and cardiovascular disease in PubMed.gov today results in a listing of 283 with the earliest publication dated 1997. From these publications, we have narrowed down search criteria by limiting to the below mentioned categories presented in the current review. The keywords used as below:

i) Epigallocatechin gallate and atherosclerosis.
ii) Epigallocatechin gallate and cardiac hypertrophy and heart failure.
iii) Epigallocatechin gallate and myocardial infarction (MI).
iv) Epigallocatechin gallate and diabetes, metabolic syndrome, and obesity.
v) Epigallocatechin gallate and anti-inflammatory effects.
vi) Epigallocatechin gallate and antioxidant effects.
vii) Metabolism and pharmacokinetics of Epigallocatechin gallate.
viii) Toxicological studies of Epigallocatechin gallate.
ix) Miscellaneous effects.
   a. *Epigallocatechin gallate and cerebral ischemia reperfusion (I/R) injury.*
   b. *Epigallocatechin gallate and fibrosis.*

2.1. Epigallocatechin gallate

Camellia sinensis is a plant in which its leaves are used to make green tea or black tea. The difference between green tea and black tea is that the oxidation process does not take place in the production of green tea. Due to the lack of steaming process, green tea is found to have a relatively high polyphenol content compared to black tea (Hu et al., 2009). These polyphenols consist of a number of phenolic rings and EGCG is known as the most abundant (nearly 40% of the total polyphenol content) and the most active chemical component which belongs to this family. According to studies, polyphenols are powerful antioxidants and cancer chemopreventive agents (Zaveri, 2006). They play a role in neutralizing free radicals, reducing inflammation and slowing down the growth of tumor.

2.2. Pharmacological action of Epigallocatechin gallate

2.2.1. Epigallocatechin gallate and atherosclerosis

Atherosclerosis is a disease of arteries that is due to endothelial dysfunction, inflammatory vascular cells and lipid accumulation (Hansson, 2009). Plaque which is usually made of fatty substances

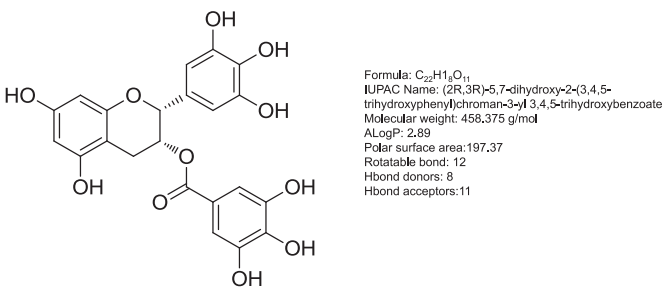

Fig. 1. Structure and properties of Epigallocatechin gallate (EGCG).