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Review

New insights into the ameliorative effects of ferulic acid in pathophysiological conditions

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ABSTRACT

Ferulic acid, a natural phytochemical has gained importance as a potential therapeutic agent by virtue of its easy commercial availability, low cost and minimal side-effects. It is a derivative of curcumin and possesses the necessary pharmacokinetic properties to be retained in the general circulation for several hours. The therapeutic effects of ferulic acid are mediated through its antioxidant and anti-inflammatory properties. It exhibits different biological activities such as anti-inflammatory, anti-apoptotic, anti-carcinogenic, anti-diabetic, hepatoprotective, cardioprotective, neuroprotective actions, etc. The current review addresses its therapeutic effects under different pathophysiological conditions (eg. cancer, cardiomyopathy, skin disorders, brain disorders, viral infections, diabetes etc.).

Contents

Abbreviations: AAPH, 2,2′-azobis (2 amidinopropane) dihydrochloride; Aβ, Amyloid β; AD, Alzheimer's disease; AGE, Advanced glycation end product; ALP, Alkaline phosphatise; ALT, Alanine aminotransferase; APC, Antigen presenting cell; APP, Amyloid precursor protein; ARE, Antioxidant responsive element; ASK1, Apoptosis signal-regulating kinase 1; AST, Aspartate aminotransferase; BAD, Bcl-2-associated death promoter; BBB, Blood brain barrier; Bcl-2, B-cell lymphoma 2; BR, Bilirubin; BRB, Blood retinal barrier; BV, Biliverdin; BVR, Biliverdin reductase; CAT, Catalase; CEP2, Centrosomal protein 2; COX, Cyclooxygenase; CREB, cAMP Responsive Element Binding; CYP2E1, Cytochrome P450 2E1; DB, Diosbulbin B; DC, Dendritic cells; DM, Diabetes mellitus; DN, Diabetic neuropathy; DR, Diabetic retinopathy; EGFR, Epidermal growth factor receptor; ELISA, Enzyme linked immunosorbent assay; ERK, Extracellular signal-regulated kinase; FA, Ferulic acid; FAA, Feruloyl-L-arabinose; FAEE, Ferulic acid ethyl ester; GABAB1, Gamma-aminobutyric acid B receptor 1; GFAP, Glial fibrillary acidic protein; GLUT4, Glucose transporter type 4; GPx, Glutathione peroxidase; GSK3β, Glycogensynthase kinase 3β; GST, Glutathione S-transferase; HF, He-Ying-Qing-Re Formula; HG, high glucose; HIF-1-α, Hypoxia-inducible factor 1-alpha; HO, Hemeoxygenase; HPLC, High performance liquid chromatography; HUVEC, Human umbilical vein endothelial cells; Iba-1, Ionized calcium-binding adapter molecule 1; ICAM-1, Intercellular adhesion molecule-1; iNOS, Inducible nitric oxide synthase; IFNγ, Interferon-γ; IGF-1, Insulin-like growth factor 1; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; IL-17, Interleukin 17; JNKs, c-Jun N-terminal kinase; Keap1, Kelch-like ECH-associated protein 1; LPS, Lipopolysaccharide; MAG, Myelin-associated glycoprotein; MAPKs, Mitogen-activated protein kinases; MBP, Myelin basic protein; MCAO, Middle cerebral artery occlusion; MCP-1, Monocyte Chemoattractant Protein-1; MMP, Mitochondrial membrane permeabilization; MMPs, Matrix metalloproteinases; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSCs, Mesenchymal stromal cells; MT, Metallothioneins; mTOR, the mammalian target of rapamycin; NFκB, Nuclearfactor kappa B Inhibitor of kappa B IκB; NOS, Nitric oxide synthase; NO, Nitric oxide; Nrf2, NF-E2-related factor; 6-OHDA, 6-hydroxydopamine; PARP, Poly (ADP-ribose) polymerase; PBMCs, Peripheral blood mononuclear cells; PD, Parkinson's disease; PGE2, Prostaglandin E; PI3K, Phosphoinositide-3 kinase; PKC, Protein kinase C; PQ, Paraquat; PS, Phosphatidylserine; RABGAP1, RAB GTPase Activating Protein 1; RANKL, Receptor activator of nuclear factor kappa-B ligand; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; ROT, Rotenone; RSK, Ribosomal s6 kinase; SLN, Solid lipid nanoparticles; SOD, Superoxide dismutase; SRXN1, Sulfiredoxin 1; TGF-β1, Transforming growth factor beta 1; TBARS, Thiobarbituric acid; T2FA, Tacrine 2-ferulic acid; TLR, Toll-like receptor; TNBS, 2,4,6-Trinitrobenzenesulfonic acid; TNF-α, Tumor necrosis factor-α; TXNRD1, Thioredoxin reductase 1; UGT, UDP-glucuronosyltransferase; VEGF, Vascular endothelial growth factor.

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1. Introduction

Natural antioxidants exhibit their therapeutic potential in various pathophysiological conditions (Bhattacharya et al., 2013; Pal et al., 2014; Rashid and Sil, 2015; Ronchetti et al., 2009; Sinha et al., 2015). Ferulic acid (FA) (4-hydroxy-3-methoxycinnamic acid) is a natural phytochemical (Fig. 1) which is obtained from rice, wheat, barley, orange, coffee, apple, peanuts etc (Chowdhury et al., 2016). FA exhibits antioxidant properties through lipid peroxidation and free radical scavenging, by its phenolic hydroxyl group (Srinivasan et al., 2007). The current review provides new insights into the mechanism of action of FA in various pathophysiological conditions. The review also emphasizes on the protective role of the molecule through modulation of signaling pathways involving Nrf2, p38, MMP and mTOR. A detailed understanding of the therapeutic applications of FA will help in the progression of studies related to this molecule in the field of clinical biology.

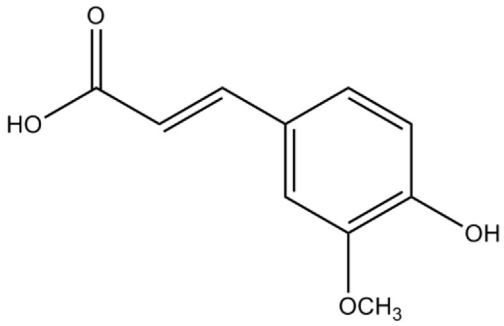

Fig. 1. Structure of ferulic acid.

2. Molecular properties of ferulic acid

Ferulic acid (FA) (4-hydroxy-3-methoxycinnamic acid) is a derivative of curcumin. It is widely found in fruits, vegetables, coffee and beer (D'Archivio et al., 2007). It is an antioxidant which has the ability to scavenge free radicals and prevent lipid peroxidation and apoptotic cell death (Fetoni et al., 2010). FA protects against reactive nitrogen species (RNS) by downregulating NOS isoforms (Koh, 2012a) and inhibits toxicity of secondary free radicals as well (e.g., those generated by carbon tetrachloride, CCl_4) (Srinivasan et al., 2005).

While reacting against a free radical, the hydrogen atom of FA is easily transferred to the radical, forming a phenoxy radical which is highly stabilized since the unpaired electron may not only be present on the oxygen but can also be delocalized across the entire molecule. Unable to elicit a radical chain reaction, this phenoxy radical gets condensed with another ferulate radical to yield the dimer curcumin. Other dimers are also formed through the condensation of the phenoxy radical with other radicals. FA binds to the lipid bilayer of cells, thereby protecting against lipid peroxidation through the use of its carboxylic acid group as an anchor. Due to generation of this phenoxy radical, FA is able to scavenge and stop free radical chain reactions (Graf, 1992; Kanski et al., 2002; Paiva et al., 2013).

It prevents free radical mediated damage by regulating the activity of hemeoxygenase/biliverdin reductase (HO/BVR) system, chaperone heat shock protein (Hsp 70), superoxide dismutase (SOD) and catalase (CAT) (Mancuso and Santangelo, 2014).

Heme oxygenase-1 degrades heme thereby generating ferrous iron, carbon monoxide (CO) and biliverdin (BV). BV is reduced by BVR to bilirubin (BR) (Maines, 1997). BR is an efficient reactive oxygen species (ROS) and RNS scavenger (Mancuso et al., 2012). FA up regulates the expression of HO-1 in rat neurons to protect against ROS associated oxidative damage (Calabrese et al., 2008). It also modulates HO-1 activity by regulating the expression and ERK mediated translocation of the transcription factor NFE2 related factor (Nrf2) to the nucleus, where it binds to the antioxidant