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Invited Review

The effects of bioactive compounds from plant foods on mitochondrial function: A focus on apoptotic mechanisms

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ABSTRACT

Mitochondria are essential organelles for cellular integrity and functionality maintenance and their imparement is implicated in the development of a wide range of diseases, including metabolic, cardiovascular, degenerative and hyperproliferative pathologies. The identification of different compounds able to interact with mitochondria for therapeutic purposes is currently becoming of primary importance. Indeed, it is well known that foods, particularly those of vegetable origin, present several constituents with beneficial effects on health. This review summarizes and updates the most recent findings concerning the mechanisms through which different dietary compounds from plant foods affect mitochondria functionality in healthy and pathological *in vitro* and *in vivo* models, paying particular attention to the pathways involved in mitochondrial biogenesis and apoptosis.

Abbreviations: AA, arachidonic acid; ADP, adenosine diphosphate; AIF, apoptosis-inducing factor; AMPK, AMP-activated protein kinase; ANT, adenine nucleotide translocase; Apaf-1, apoptotic protease activating factor-1; ATP, adenosine triphosphate; ATP-ase, ATP synthase; AZT, azidothymidine; BH, Bcl-2 homology; CA, caffeic acid; CACT, carnitine/acylcarnitine translocase; CAD, caspase-activated DNase; CAPE, caffeic acid phenetyl ester; CAT, catalase; cIAP, cellular inhibitor of apoptosis protein; CL, cardiolipin; COX, cyt c oxidase; CPT, carnitine palmitoyl transferase system; CPT1, carnitine palmitoyl transferase 1; CPT2, carnitine palmitoyl transferase 2; CREB, cAMP response element; CSA, cyclosporin A; Cy, cyanidin; Cy3G, cyanidin-3-glucoside; cyt c, cytochrome c; DHA, docosahexaenoic acid; DIABLO, direct IAP-binding protein with low pI; DISC, death inducing signaling complex; DOX, doxorubicin; Dp, delphinidin; Dp3G, delphinidin-3-glucoside; EA, ellagic acid; EGC, epigallocatechin; EGCG, epigallocatechingallate; Endo G, endonuclease G; EPA, eicosapentaenoic acid; ERKs, extracelular signal-regulated kinases; ETC, electron transport chain; Exe, excessive exercise; FADD, Fas-associated death domain; FasL, Fas ligand; FOXO3, Forkhead box O3; GCL, γ-glutamyl-cysteinyl-ligase; GPX, glutathione peroxidase; GSH, glutathione; GSPE, grape seed procyanidin extract; GSPs, grape seed proanthocyanidins; GSSG, glutathione disulfide; H_2O_2, hydrogen peroxide; HepG2, hepatocellular carcinoma cells; HKs, hexokinase; HO-1, heme-oxygenase-1; HT, hydroxytyrosol; IAP, inhibitors of apoptosis proteins; IkB, inhibitors of NF-kB; IL, interleukin; IMM, inner mitochondrial membrane; IMS, intermembrane space; JNKs, c-Jun N-terminal kinases; MAPKs, mitogen activated protein kinases; Mcl-1, myeloid leukemia cell differentiation protein; MMP, mitochondria membrane permeabilization; MnSOD, manganese superoxide dismutase; MPTP, mitochondrial permeability transition pore; mRNA, messenger RNA; mtDNA, mitochondrial DNA; mTOR, mammalian target of rapamycin; mtROS, mitochondrial ROS; MUFAs, monoinsatured fatty acids; Mv, malvidin; Mv3G, malvidin-3-glucoside; n-3/6 PUFAs, n-3/n-6 polyinsaturated fatty acids; NF-kB, nuclear factor kB; NO, nitric oxide; NQO-1, NADPH-quinone oxidoreductase I; NRF1 and NRF2, nuclear respiratory factors 1 and 2; Nrf2, nuclear factor-E2-related factor 2; $O_2^{\cdot-}$, superoxide radical; OGD, oxygen–glucose deprivation; OMM, outer mitochondrial membrane; $ONOO^-$, peroxynitrite; OO, olive oil; OPP, ortho-phenylphenol; OXLDL, oxidized low density lipoproteins; OXPHOS, oxidative phosphorylation; p38 MAPK, p38 mitogen-activated protein kinase; PA, roanthocyanidin; PARP, poly (ADP-ribose) polymerase; PBR, peripheral benzodiazepine receptor; PDH, pyruvate dehydrogenase; Pg, pelargonidin; Pg3G, pelargonidin-3-glucoside; PGC-1α, peroxisome proliferator-activated receptors coactivator 1α; PI3K, phosphatidylinositol 3-kinase; PKB or AKT, protein kinase B; POPAs, purificated oligomeric proanthocyanidines; PPARs, peroxisome proliferator-activated receptors; RCR, respiratory control ratio; RNS, reactive nitrongen species; ROS, reactive oxygen species; RV, resveratrol; SAPKs, stress-activated protein kinases; SIRT1, sirtuin 1; Smac, second mitochondria-derived activator of caspases; SO, safflower oil; SOD, superoxide dismutase; tBid, truncated Bid; TCA, tricarboxylic acid cycle; TCC, tricarboxylate carrier; TF, theaflavins; TFAM, mitochondrial transcription factor A; TFB2, mitochondrial transcription factor B2; TNF, tumor necrosis factor; TNF-R, tumor necrosis factor receptors; TNF-α, tumor necrosis factor α; TR, thearubigins; UCP, uncoupling proteins; VDAC, voltage dependent anion channel; XIAP, X-linked inhibitor of apoptosis protein; YY1, ying yang 1 transcription factor; α-LNA, α-linolenic acid; α-TOS, α-tocopheryl succinate; $\Delta\Psi m$, mitochondrial membrane potential.

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1. The mitochondrial kingdom

Mitochondria are the cell main energy producers and are therefore essential for normal cellular functions, including intracellular metabolic activities and signal transduction of various cellular pathways. The predominant physiological function of mitochondria is the generation of adenosine triphosphate (ATP) by oxidative phosphorylation (OXPHOS), but additional functions include the generation and the detoxification of reactive oxygen species (ROS), the involvement in some forms of apoptosis, the regulation of cytoplasmic and mitochondrial matrix calcium, the synthesis and the catabolism of metabolites and the transport of the organelles themselves to correct locations within the cell (Camara et al., 2010; Brand and Nicholls, 2011). A variety of these mechanisms regulated by mitochondria are strongly implicated in the control of cellular redox potential, which indicates just how oxidizing the environment inside the cell is. Cellular redox potential is critically important for normal physiological processes and its dysregulation is implicated in the initiation and proliferation of several diseases (Mallikarjun et al., 2012).

Several pathologies apparently related to mitochondria have been identified, including metabolic (e.g., type 2 diabetes), cardiovascular and neurodegenerative diseases, cancer, psychiatric disorders and aging (Camara et al., 2010; Frantz and Wipf, 2010).

A complete understanding of mitochondrial function in normal and pathological states is critical for developing the full therapeutic potential of the organelle in mitigating or preventing a given disease. Mitochondrial related diseases are extensively different, and the numerous aspects linking mitochondria to different disease states are still being studied (Camara et al., 2010).

1.1. Mitochondrial structure and functions

The elaborate structure of mitochondria is important for the normal performance of the organelle and, therefore, constitutes a potential therapeutic target. It is comprised of four distinct compartments that carry out specialized functions: the outer mitochondrial membrane (OMM), the intermembrane space (IMS), the inner mitochondrial membrane (IMM), and the mitochondrial matrix (Frantz and Wipf, 2010; Camara et al., 2010).

1.1.1. Outer mitochondrial membrane

The OMM borders the narrow IMS and contains many channels formed by the protein porin that makes the membrane relatively permeable. The constituents inside the OMM include the peripheral benzodiazepine receptor (PBR), the voltage dependent anion channel (VDAC), other translocated proteins such as hexokinases (HKs), the Bcl family of proteins, such as Bax and Bak (Camara et al., 2010) and the translocase of the outer membrane (TOM complex) (Künkele et al., 1998; Becker et al., 2005).

PBR is a small evolutionarily conserved protein involved in cholesterol transport and steroid synthesis. It is also concerned with OMM permeabilization by interaction with the pro-apoptotic Bcl family proteins and it is found to be in close association with the VDAC. VDAC is a mitochondrial protein synthesized by the nuclear genome and is the principal site for exchange of metabolites, such as ATP, between the IMS and the cytosol (Okada et al., 2004). As a principal portal in and out of the mitochondrion, VDAC mediates a close dichotomy between metabolism and death in all type of cells (Lemasters and Holmuhamedov, 2006; Camara et al., 2010). Also HKs exert a crucial role in promoting cell survival. In particular, HK I and II mediate cytoprotection by binding specifically to the VDAC, in part via the hydrophobic N terminus specific residues of VDAC in the presence of Mg^{2+}. In tumor cells this association between HK and VDAC provides extra protection against permeabilization of the OMM and resistance to apoptosis (Camara et al., 2010). During the activation of cell death programs, permeation of the OMM takes place also through the activation of Bax and Bak proteins, which are located in cytosol and translocate to the OMM as a consequence of oxidative stress. In this way, the restricted permeability of the OMM protects against cell damage and cell death due to oxidative stress (Camara et al., 2010).

The TOM complex involves the protein-conducting channel Tom40, which is its central component, the receptor proteins