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Original Article

Effects of physical exercise and plant polyphenols on human mitochondrial health

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Abstract
Physical activity combined with a polyphenols rich diet have been recently emerged as a non-pharmacological approach able to prevent and/or ameliorate symptoms that are related to the disfunctions of energy-related health processes, in particular during aging. In this article we first described the key role of mitochondrial functions in energy production systems that are activated during different types of physical activity. Then, we have reported some relevant and recent aspects concerning aging-related mitochondrial disfunctions involved in several human diseases, providing an overview of the most relevant *in vivo* and *in vitro* studies. These studies aimed to the identification of molecular mechanisms causing mitochondrial disfunctions including mitochondrial DNA mutations, radical oxygen species (ROS) generation and oxidative stress, that led to aging-related sarcopenia. These results explored the major approaches used for the prevention and the treatments of mitochondrial diseases. In particular, we have highlighted the effects of physical exercise and plant polyphenols on mitochondrial function in the aerobic mechanism of ATP synthesis. In fact, the secretion of myokines from contracting skeletal muscle allows the modulation of various metabolic processes and can improve mitochondria cell and bioenergetic functions. Polyphenol intake has been shown to counteract several aging-related alterations including inflammation and oxidative stress, and therefore we describe the effects of these molecules, also in pure form, as food integration, and we have also summarized their effects on mitochondrial functions. Finally, we have reviewed the state of art of these strategies focusing on both physical exercise and plant polyphenols-rich diet based approaches on skeletal muscle mitochondrial health in humans that aim to prevent and counteract aging-related diseases.
Keywords: energy system; mitochondrial disfunctions; antioxidant; polyphenols; myokines; emerging approaches.

Introduction

Among different types of physical activities, the physical exercise and sport activity require huge amounts of bioavailable energy that is specifically used for the contraction of skeletal muscle (Glancy & Balaban, 2021; Barclay, 2015; Glaister, 2005). Muscle contraction utilizes the energy that is released as a consequence of adenosine triphosphate (ATP) phospho-anhydride bond breakdown. Since the muscle ATP concentration available is not sufficient to ensure continuous contraction, the cells synthesize new ATP molecules by means of three main systems, summarized in Table 1. These different systems are activated in a sequential and coordinate manner during exercise depending from its intensity and duration.

Table 1: Physical exercise and bioenergetic systems

Exercise Type	Mechanism	Energy System	Substrates	Reactions and Metabolic Pathway
High intensity – Short time	Anaerobic mechanism	Phosphagen system	Phosphocreatine ADP	- Creatine kinase - Adenylate Kinase (Myokinase)
		Lactate production	Glucose (glycogen store)	- Glicolysis - Homolactic fermentation
Moderate intensity – Prolonged time	Aerobic mechanism	Complete aerobic oxidation	Glucose (glycogen store)	- Glicolysis - Krebs Cycle - Oxidative Phosphorylation
			Free Fatty acids	- Beta-oxidation - Krebs Cycle - Oxidative Phosphorylation
			Amino acids	- Transamination and oxidative deamination - Urea Cycle - Krebs Cycle - Oxidative Phosphorylation

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These pathways include ATP formation by both substrate-level phosphorylation via creatine-kinase or adenylate kinase (anaerobic mechanism) and/or oxidative phosphorylation (OXPHOS) in the aerobic mechanism that can use glucose, fatty acids and amino acids as substrates. Exercise lasting over 60 s requires oxygen for complete substrate oxidation to carbon dioxide and maximal ATP production (Glaister, 2005; Barclay, 2015).

Inside the eukaryotic cells, the mitochondria represent the cell energy centre as they are the site of the OXPHOS system. Mitochondria are double membrane wrapped intracellular organelles responsible for the major amount of ATP production that is required for all cell metabolic processes including growth and proliferation. The membrane system delimiting the mitochondrion is constituted by two different specialised membranes that delimitate two separated compartments: the inter-membrane space and the mitochondrial matrix. While the composition of the inter-membrane space is chemically equivalent to that of the cytosol in terms of the small molecules contained, the composition of the mitochondrial matrix is rather different as it shows *i)* a gel-like consistency, due to high concentration of water-soluble proteins; *ii)* the presence of several enzymes, in particular those catalysing the various steps of the tricarboxylic acid cycle (Krebs cycle), *iii)* ribosomes and double-stranded circular DNA molecules, encoding for a small number of proteins involved in the electrons transport, for two ribosomal RNAs and for about 20 tRNAs.

The OXPHOS system is located in the inner mitochondrial membrane and consists of the complexes of the electron transport chain (ETC) and the ATP synthase. The four complexes of the ETC are complex I (NADH–ubiquinone oxidoreductase), complex II (succinate–quinone oxidoreductase), complex III (ubiquinol–cytochrome *bc1* oxidoreductase), and complex IV (cytochrome *c* reductase). Using ubiquinone and cytochrome *c*, these complexes couple electron transport with proton pumping to generate a gradient that is used by ATP synthase to phosphorylate ADP and produce ATP. The electrons transport to molecular oxygen, is associated to the generation of a chemo-osmotic gradient across the mitochondrial inter-membrane space and matrix, whose restoration generated the energetic requirement for ATP synthesis by the ATP synthase. The electron transport system includes four metal ions containing protein complexes and two non-ionic electron carriers: ubiquinone and cytochrome *c*.

Several studies reported that mitochondria DNA alterations can occur causing mitochondrial genetic disorders, leading to the failing in producing enough energy for cells to function and/or to cell death, via apoptosis (Reinecke et al., 2009; Koopman et al., 2013; Ghezzi & Zeviani, 2018; Hock et al., 2020; Tang et al., 2020; Fernandez-Vizarra & Zeviani, 2021). Generally, the mitochondrial diseases can involve both child and adult but the prevalence of them is different, because in child they are essentially due for consanguinity, and for recessive mutations in POLG (Rahman & Copeland, 2019), a protein coding gene, for the catalytic subunit of DNA polymerase gamma (pol γ). Vice versa, in adults no consanguineous component can be found, and only other mutations in mitochondrial DNA (mtDNA) and in nuclear DNA (nDNA) (Gorman et al., 2016) can occur. In the elderly, different mitochondrial diseases lead to a progressive loss of skeletal muscle mass and functions, a condition defined sarcopenia (Larson et al., 2019).

The main reason for the occurring of the mitochondrial DNA mutations can be linked to the presence of radical oxygen species (ROS), namely the superoxide anion $O_2^{\bullet -}$, the hydrogen peroxide H_2O_2 and the hydroxyl radical $OH^{\bullet}$, species extremely reactive and toxic which were formed through incomplete oxygen reduction according to the following reactions:

$$O_2 + e^- \longrightarrow O_2^{\bullet -}$$

$$O_2 + 2H^+ + 2e^- \longrightarrow H_2O_2$$

$$O_2 + 3H^+ + 3e^- \longrightarrow H_2O + OH^{\bullet}$$

The production of ROS in mitochondria during respiratory chain is normally occurring (Chen et al., 2022), and therefore, different enzymes such as superoxide dismutase, catalase, glutathione peroxidase or antioxidant molecules, called scavengers, are functioning to neutralize and inactive them.

When the production is abnormal and the ROS accumulates, their toxic effects became visible. In particular, many molecules inside the mitochondria can be the target of oxidation reactions; for instance those involving lipid membranes can cause the formation of pores that in turn can modify the mitochondrial DNA leading to mutations (Gorman et al., 2016). These mutations produce alterations in the structure, and then in the function, of the mitochondrial respiratory chain components or in the organelle protein synthesis machinery.

The diagnosis of mitochondrial diseases is quite complicated, because of the expression of diversified clinical symptoms and phenotypes related to mtDNA mutations. An initial diagnosis can be done through the evaluation of the levels of selected mitochondrial biomarkers in blood, urine, and spinal fluid, but its correlation to the disease is not yet well characterized (Parikh et al., 2015). Primary mitochondrial disorders are caused by mutations in the maternally inherited mtDNA leading to an heteroplasmy in its structure where wild type mtDNA paternally inherited is mixed up with mutated maternally obtained mtDNA. The detection of heteroplasmy can be done thanks to the new next-generation sequencing (NGS) technology which become the gold standard for the evaluation of mitochondrial diseases. This new method shows a great sensitivity in

discovering point mutations, heteroplasmy, and deletions (Parikh et al., 2015). Obviously, if the disease is multisystemic it may be necessary to carry out these analyses in the different organs affected. However, other useful methods have been applied in the recent past for researching deletions in mtDNA such as Southern Blotting and comparative genome hybridization but the low sensitivity limitation has led to the recent replacement with NGS.

Material & Methods

The source articles were identified through the web database query PubMed, Scopus and Web of Science as tool for searching in the biomedical literature, searching in particular for the topics related to energy system during physical exercise, mitochondrial health and disfunctions, plant polyphenols effects. The keywords used for the web data base query included: energy system; mitochondrial disfunctions; antioxidant; polyphenols; myokines; emerging approaches. The search results were analyzed in reverse chronological order and restricted to the last 15 years, and, the relevant refences limited to peer-reviewed article were consulted.

Results

Prevention and the treatments of mitochondrial diseases

To prevent, delay or treat mitochondrial diseases, several approaches are available**.** Therapeutic approaches for most mitochondrial diseases have been mostly limited to symptom specific therapies and supportive measures including exercise and dietary supplements, such as vitamins, polyphenols, cofactors and antioxidants (Almannai et al., 2020). However, over the past few years, the number of preclinical and clinical trials in mitochondrial disorders have been increased, aiming for more specific and effective therapies (Schon et al., 2018; Almannai et al., 2020).

The pharmacological approach was based on vitamin and cofactor administration, but also a variety of novel compounds, many of which are in clinical trials (Pitceathly et al., 2021). This approach acts on different disease mechanisms and can be broadly divided in the use of: antioxidants molecules, vitamins and molecules involved in enzyme activity.

Antioxidant molecules

Supplementation with CoQ10 (ubiquinone), an integral component of the mitochondrial electron transport chain (ETC), in primary CoQ10 deficiency, led to electron flow restoring and to an improvement in clinical manifestations. It was suggested that CoQ10 supplementation to individuals with other mitochondrial diseases would improve the efficacy of electron transfer through ETC (El-Hattab et al., 2017; Almannai et al., 2020).

Idebenone, a CoQ10 analog, with a higher efficacy and more favorable pharmacokinetic profile, is a molecule currently approved for treating Leber hereditary optic neuropathy (LHON) in Europe but is not FDA approved (El-Hattab et al., 2017; Pitceathly et al., 2021).

EPI-743, a novel para-benzoquinone analog, exerts its antioxidant effects through repletion of reduced intracellular glutathione. In an open-label study with patients with a heterogeneous group of mitochondrial disorders, EPI-743 was associated with clinical improvement in most subjects treated (El-Hattab et al., 2017; Aliotta et al., 2020; Almannai et al., 2020).

Elamipretide, a mitochondrial-targeted tetrapeptide that associates with cardiolipin in the inner mitochondrial membrane, is involved the mitochondrial cristae structure, promotes oxidative phosphorylation, and reduces ROS production (Almannai et al., 2020).

Recently, Sonlicromanol (KH176) was developed as an orally bioavailable small molecule that works as an antioxidant as well as a redox modulator (Almannai et al., 2020).

Lipoic acid, an essential coenzyme of the pyruvate dehydrogenase and ketoglutarate dehydrogenase, is often administered with other antioxidants to individuals with mitochondrial diseases (El-Hattab et al., 2017).

Glutathione is a major intracellular antioxidant and its synthesis depends on the availability of cysteine. As glutathione deficiency can occur in mitochondrial diseases, supplementation with cysteine donors can potentially restore glutathione levels and therefore enhance elimination of excessive ROS in mitochondrial diseases (El-Hattab et al., 2017). N-acetylcysteine also increases cysteine availability and glutathione synthesis, and has been tried in ethylmalonic encephalopathy (El-Hattab et al., 2017).

Besides, compounds increasing of mitochondrial biogenesis have also been investigated such as:

- bezafibrate, a pan-PPAR agonist that activates the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) axis, was tested in fibroblasts from patients with heterogeneous mitochondrial diseases and the results demonstrated a stimulation of PGC1α and improved mitochondrial respiratory chain defects (Hirano et al., 2018; Cerchia et al., 2019; Almannai et al., 2020).
- an AMP analog, the 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) is able to induce PGC-1α-dependent mitochondria biogenesis through the activation of the AMP-dependent kinase (AMPK) as well as to induce the regeneration of muscle fibers making it a potential therapeutic target in mitochondrial disorders (Hirano et al., 2018; Almannai et al., 2020; Bottani et al., 2020).

Vitamins and molecules involved in enzyme activity

- Riboflavin (vitamin B2), a flavoprotein precursor that is an essential component in complexes I and II, and a cofactor in key enzymatic reactions involved in the fatty acid β-oxidation and the Krebs cycle. Multiple acyl-

CoA dehydrogenase deficiency, typically caused by electron-transport flavoprotein dehydrogenase (ETFDH) gene mutations, is an inborn error of metabolism involving several of these enzymatic reactions, and riboflavin supplementation can ameliorate its symptoms and slow its progression.
Further, the riboflavin supplementation ameliorates symptoms caused by complex I and acyl-CoA dehydrogenase-9 (ACAD9) deficiencies (El-Hattab et al., 2017).
- Thiamine (vitamin B1) also enhances pyruvate dehydrogenase activity, thereby increasing the pyruvate oxidation and the production of reduced cofactors (NADH and $FADH_2$). Thiamine has been used in mitochondrial disorders individually or in combination with other agents (El-Hattab et al., 2017).
- Dichloroacetate is able to induce the activation of the pyruvate dehydrogenase enzyme by the inhibition of pyruvate dehydrogenase kinase, that normally phosphorylates and inhibits the enzyme. As result, the conversion of pyruvate to acetyl-CoA is increased allowing an activation of the Krebs cycle thus producing ATP through the oxidative phosphorylation. Therefore, dichloroacetate has been used to treat lactic acidosis in mitochondrial diseases (El-Hattab et al., 2017). In addition, the supplementation with creatine monohydrate can improve exercise capacity in some individuals with mitochondrial myopathies as well as arginine and citrulline can have therapeutic utility in treating nitric oxide (NO) deficiency-related manifestations of mitochondrial diseases (El-Hattab et al., 2017).

Physical exercise approach and myokines

Several studies have demonstrated that physical exercise can induce beneficial effect that counteracts mitochondrial diseases (Voet et al., 2013; Tarnopolsky et al, 2014). In particular, aerobic endurance training can increase mitochondrial number, by stimulating mitochondrial biogenesis, and increasing muscle mitochondrial enzyme activities and muscle strength (Taivassalo et al., 2006). Endurance training can activate mitochondrial proliferation through induction of PGC-1α, the master transcriptional regulator of mitochondrial biogenesis (Rowe et al. 2012). It seems able to regulate not only PGC1α but also PGC1β, AMPK, p38 MAPK and the hypoxia inducible factors (HIFs), factors leading to the extensive metabolic and molecular remodeling to the preservation of aerobic fitness and muscle strength. Also, physical activity upregulates endothelial nitric oxide synthase (eNOS) gene expression leading to an increase of nitric oxide (NO) production, which in turn induces mitochondrial biogenesis El-Hattab et al., 2017; Hirano et al., 2018; Bottani et al., 2020). Furthermore, it has been suggested that resistance training in individuals with mtDNA mutations can lead to an overall reduction in the proportion of mutated mtDNA. Mutated mtDNA are often undetectable in muscle satellite cells, which are committed myogenic cells reactivated as needed for muscle growth and repair. So it has been proposed a method for normalizing the skeletal muscle mtDNA genotype in patients with mitochondrial myopathies, based on the stimulations of the proliferation and incorporation of satellite cells into existing myofibers through exercise training with encouraging results (El-Hattab et al., 2017; Vitucci et al., 2018; Bottani et al., 2020).
In addition, clinical studies have shown that rehabilitation endurance training increased maximal oxygen uptake, work output, minute ventilation, endurance performance, walking distance in shuttle walking test, peripheral muscle strength, and improved clinical symptoms in patients with mitochondrial myopathies (Tarnopolsky et al., 2014; Bottani et al., 2020]. Therefore, a combination of progressive endurance with or without resistance exercise should be recommended to mitochondrial patients (Hirano et al., 2018).

Since during physical exercise the demand for ATP synthesis is increased, the contracting skeletal muscle produces numerous myokines, that induce cellular and metabolic effects on different tissues and organs (Pedersen & Febbraio, 2012). Myokines are proteins, that like hormones, regulate metabolic homeostasis, muscle regeneration, modulate the aging process and are also involved in mitochondria function regulation (Pedersen 2016; Pang et al., 2021). Among myokines, some show positive effects on mitochondria fusion, metabolism and biogenesis including Interleukin-15 (IL-15) Interleukin-6 (IL-6), Brain-Derived Neurotrophic Factor (BDNF) Fibroblast Growth Factor 21 (FGF21), Irisin, Myostatin through activation of specific signal transduction pathways (Thornton et al., 2016; Pang et al., 2021).

Dietary approaches and polyphenols

Dietary approaches and mitochondrial functions

Although no specific nutritional therapy can be used to treat mitochondrial disorders, some diets rich in specific components and nutritional supplements may improve some symptoms (Kuszak et al., 2018). Zweers et al. (2021) reported that primary mitochondrial disorders (PMD) that have epilepsy as a common feature can ameliorate following a ketogenic diet can control seizures with an unclear mechanism. Ketogenic diet has proposed in patients with inborn errors of pyruvate dehydrogenase complex (PDC), given the alternative production of acetyl-CoA from ketone bodies rather than pyruvate. They showed increased longevity and improved mental development. Ketonic bodies also increased OXPHOS genes expression leading to the activation of many transcription factors and cofactors, such as AMPK, SIRT1, and PGC-1α, with consequent increase of mitochondrial biogenesis. Even for complex I defects, ketogenic diet could have beneficial effects, promoting mitochondrial respiration through complex II (CII) activity and the oxidation of $FADH_2$, bypassing the inactive CI (Bottani et al., 2020; Landi et al., 2021; Zweers et al. 2021). Therefore, a high-lipid, low-carbohydrate diet can improve oxidative phosphorylation capacity to treat mitochondrial diseases.

Polyphenols and mitochondrial functions

Polyphenols have been considered the main natural compounds with anti-inflammatory, anti-cancer properties (Pagliara et al., 2018; Pagliara et al., 2019; Pagliara et al., 2021) and they are also able to inhibit enzymes such as acetyl-cholinesterase and mono-amine oxidase involved in neurodegenerative disorders (Alcaro et al., 2007; Nasso et al., 2021; Costanzo et al., 2021). In addition, natural polyphenols can modulate mitochondrial functions, as activation of mitochondrial biogenesis (Chodary et al., 2021).

Among natural polyphenols, epicatechin, founded in high concentration in dark chocolate, has mitochondrial biogenic properties. Indeed, mice fed with epicatechin demonstrated improved exercise performance and fatigue resistance, enhanced mitochondrial biogenesis with increased electron transport chain (ETC) proteins, mitofilin, porin, mitochondrial transcription factor A (TFAM), mitochondrial volume, and cristae abundance (El-Hattab et al., 2017; Ferrara et al., 2021). Hydroxytyrosol (HT), founded in olives and extra virgin olive oils, activates PGC-1α through SIRT1 de-acetylation and induced mitochondrial biogenesis in vitro and in skeletal muscle in vivo. Prolonged HT administration significantly activated AMPK, SIRT1, and PGC-1α in db/db mice. Moreover, hydroxytyrosol stimulated NRF-1 and TFAM and increased mitochondrial DNA content and ATP synthesis (Bottani et al., 2020; Pagliara et al., 2020; Chodary et al., 2021). Curcumin stimulated different mitochondrial biogenesis markers, upregulating PGC-1α and TFAM protein expression, improving MMP and ATP levels and restoring mitochondrial fusion in the brain. Curcumin has been shown to have positive effects on OXPHOS components and may be beneficial for patients harboring mitochondrial respiratory chain dysfunction (Bottani et al., 2020; Teixeira et al., 2019). Resveratrol (RSV) displays multiple interactions with mitochondrial activity, with mitogenetic, anti-oxidant, and anti-apoptotic effects (De Paepe et al., 2017; Mizuguchi et al., 2017). RSV upregulates the SIRT1-mediated mitochondrial biogenesis and the functions of other key players as AMPK and PGC-1α. Resveratrol stimulates PGC-1α activity, boosting deacetylation with SIRT1's mediation and enhancing transcriptional activity. Resveratrol's effects on mediating mitochondrial biogenesis through activation of AMP protein kinase (AMPK) have been presented in many studies. The blockade of oxidative phosphorylation (OXPHOS) complex III, phosphodiesterase, or ATP synthase by resveratrol is mainly contributed to the activation of AMPK. Resveratrol activates SIRT1, which in turn terminates in liver kinase B1 deacetylation and AMPK activation accompanied by enhancement (in vivo and vitro) of mitochondrial function. Resveratrol influences the activity of mitochondrial complex I binding to the subunits of nicotinamide adenine dinucleotide (NADH) dehydrogenase. RSV shows regulatory effects on the synthesis of ATP and complex V. Moreover, resveratrol has a role in the maintenance of cellular mitochondrial DNA replication. In patients suffering from Complex I and IV deficiency, after resveratrol administration, it was shown an increase of mitochondrial biogenesis in fibroblasts. Therefore, current evidence indicates the beneficial effects of resveratrol in OXPHOS-related diseases, by both stimulating mitochondrial proliferation and reducing cytotoxic ROS by-products and apoptotic cell signaling. Furthermore, these data promote resveratrol as a chemoprophylaxis for enhancing mitochondrial biogenesis (Bottani et al., 2020; Chodary et al., 2021).

Quercetin is a potent antioxidant flavonoid, more specifically a flavonol, which activates SIRT1 and PGC-1α and increases mtDNA and cytochrome *c* content in skeletal muscle and brain. *In vitro* findings proposed that administration of quercetin increased the mitochondrial DNA content and, in a dose-dependent manner, affected the expression level of TFAM, NRF-1, and PGC-1α. Moreover, the OXPHOS complex II, IV and V functions were also enhanced with quercetin. Hence, the collected data from experimental investigations suggest that quercetin, activating PGC-1α/NRF-1 and TFAM signaling, stimulates biogenesis of mitochondria (Bottani et al., 2020; Chodary et al., 2021). Other polyphenols contained in green tea extracts, besides inhibiting invasiveness of gastric cancer cells (Arcone et al., 2016) also exert a stimulating effect of mitochondrial biogenesis (Chodary et al., 2021).

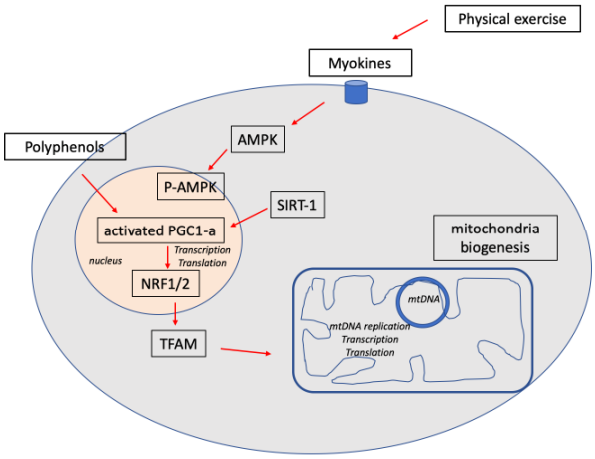

Figure 1. Schematic representation of the signaling pathways involved in mitochondrial biogenesis modulated by physical activity and diet polyphenols.

Peroxisome proliferator-activated receptor-γ coactivator-(PGC-)1α, through activation of the transcription factors, mainly NRF-1 (nuclear respiratory factor 1) and NRF-2 induces mitochondrial transcription factor A (TFAM), that promotes mitochondrial biogenesis. NRF-2 also activates mtDNA replication, transcription and protein translation Different key factors including ROS production, nitric oxide, calcineurin, AMPK (AMP-activated protein kinase), energy sensor, and sirtuins can induce PGC-1α and mitochondrial biogenesis; Silent information regulator-1 (SIRT-1).

Conclusions

Mitochondrial health is an essential requirement to ensure an adequate amount of ATP production necessary for cell homeostasis and, in particular, for skeletal muscle functions. Mitochondrial diseases, resulting from dysfunctions of mitochondrial oxidative phosphorylation process can affect energy required for all cell processes and are involved in several age-related human syndromes.

These findings confirm the beneficial effects exerted by physical exercise and diet polyphenols as preventive and/or therapeutic approaches against mitochondrial disfunctions and oxidative stress.

However, further investigations will be necessary to better elucidate the cellular and molecular mechanisms underlying effects triggered by the above approaches, to have a major impact on mitochondrial-disfunction dependent human disorders.

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