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Original Article

Modulation of mitochondrial biogenesis: action of physical activity and phytochemicals

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Abstract
Mitochondria are dynamic organelles whose centralrole is synthesis of adenosine-triphosphate (ATP)by oxidative phosphorylation. They controlseveral cellular activities such as, calcium homeostasis, apoptosis and productionof reactive oxygen species (ROS). These organelles are the focus of metabolic pathways, and mitochondrial alteration is indirectly or directly involved in the origin of manysyndromes.Increased mitochondrial ROS synthesis can perturb the activity of enzymes involved in these paths, affecting both the ATP synthesis and the metabolic responses. Mitochondrial biogenesis involves an increase in mitochondrial number and the overall capacity of oxidative phosphorylation, and it is a critical determinant of all tissues function, and in particular of skeletal muscle. Appropriate nutrition and a constant physical activity,acting on the mitochondrial biogenesis, are essential and modifiable factors that play a key role in preventing and/or delaying the mitochondrial degeneration. Exercise-induced mitochondrial remodeling is mediated by upstream signaling events that converge on downstream transcriptional co-factors, and factors that orchestrate a co-ordinated nuclear and mitochondrial transcriptional response associated with mitochondrial renovation. Furthermore, the defensiveconsequence of some natural mixtures on the mechanism involved in mitochondrial role has also been revealed. Recently a special interest has been focused on phytochemicals, food-derived bioactive compounds and nutraceuticals that might link high biological activity with good tolerance and low systemic toxicity. Polyphenols are phytochemicals found ubiquitously in plants and their regular consumption has been associated with a reduced risk of a number of chronic diseases. Newly, copiousness of evidence shows the promising role of the polyphenols on mitochondrial structure and function.Thispapersummarized the current findings concerning the capability of physical activity and selected phytochemicals to act on action of the mitochondria by the inspiration of their biogenesis.
Keywords: mitochondria, sport, polyphenol, performance, oxidative stress.

Introduction

Mitochondria (**Figure 1**) are very specialized organelles found in most eukaryotic cells, they are necessary to guarantee energy homeostasis, especially the synthesis of adenosine triphosphate (ATP) (Kausar, Wang, & Cui, 2018) moreover, they adjust several cellular functions such as apoptosis, calcium homeostasis, and the formation of reactive oxygen species (ROS).

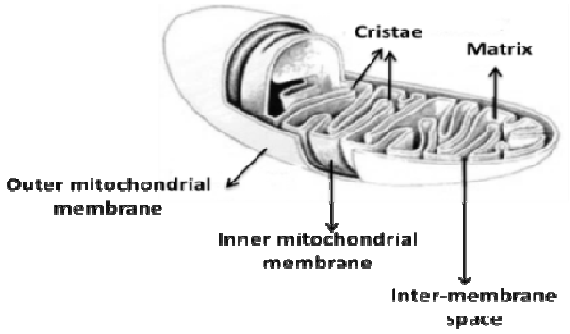

Figure 1. Section of mitochondria

The creation of ATP is carried out during the tricarboxylic acid cycle (TCA), located within the matrix, and via the electron transport system (ETS), located along the inner mitochondrial membrane. Specifically, ETS

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consists of 5 multi-polypeptide complexes (complexes I to V) embedded in the inner mitochondrial membrane that accept electrons from nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), produced mainly in the TCA cycle. During ETS, electrons are transported along complexes I to IV, with O_2 as the final acceptor at complex IV. In this process, protons are expelled out of the matrix into the inter-membrane space causing an electrochemical gradient that characterizes the driving force enabling Complex V to generate ATP by phosphorylation of adenosine diphosphate (ADP). The whole of these last two processes is defined as oxidative phosphorylation (OXPHOS) (Bishop et al., 2014). A by-product of this event is the synthesis of ROS. ROS are formed in several cellular compartments, and mitochondria are a major contributor to ROS, as they produce almost 90% of the total number of cellular ROS. So, the consumption of oxygen by aerobic organisms exposes them to the attack of reactive oxygen and nitrogen species, which can initiate chain reactions leading to oxidative damage of important biological molecules.Free radicals and ROS are the main oxidizing agents in cellular systems, and are embroiled in aging and the onset of numerous types of syndromes (D'Angelo, et al., 2013; D'Angelo et al., 2012; Ingrosso et al., 1996; Ingrosso et al., 1995). Aerobic organisms are provided with an effective antioxidant defense system that allows them to neutralize the oxidative actions of reactive metabolites of oxygen and nitrogen. However, when reactive species synthesis exceeds the cellular antioxidant capacity, oxidative stress improves, potentially leading to cell structural and functional changes and to the increase of many pathological situations.

The ETS is one main ROS producers found in skeletal muscle and exercise-induced aerobic bioenergetics reactions in mitochondria and cytosol enhances synthesis of ROSs (Chakrabarty et al., 2018). In fact, the balance of free radicals inside the skeletal muscle is very significant, principally in the context of exercise and sport as the main adaptations occur in the trained skeletal muscle, which can diverge with the type of exercise but seem to be nevertheless dependent on ROS synthesis. ROSs, maintained in physiological concentrations, are important signaling molecules that regulate growth, proliferation, and differentiation, and are responsible for some key adaptations to exercise training at the tissue and cellular levels (e.g. antioxidant enzyme regulation, mitochondrial biogenesis, and skeletal muscle hypertrophy). Thus, aerobic physical activity encourages skeletal muscle adaptive responses able to control an augmented resistance to conditions, among which prolonged or strenuous exercise, in which ROS synthesis increase. Conversely, heavy resistance exercise determines hypertrophy and augmented strength synthesis but does not alter biochemical characteristics of muscle cells (Di Meo et al., 2019). An only session of strenuous or prolonged exercise leads to the synthesis of high quantity of radicals and other ROS, which cause tissue injury and dysfunction. On the other hand, systematic exercise appears to reduction the incidence of a wide range of ROS-associated syndromes because the single sessions of a training program produce low amounts of ROS, which can induce adaptive responses beneficial for the organism. To maintain a healthy status, mitochondria regulate their biogenesis and engage in numerous dynamic behaviors. Mitochondrial biogenesis is definite as the coordinated regulation between nuclear gene expression, protein import and transcription of mtDNA. Specifically, is the cellular process that produces new mitochondria, and it's one of the ways cells adapt to the ever-changing energy requirements dictated by environmental and physiological situations (Chakrabarty et al., 2018). Cells do not generate mitochondria de novo, but instead identify and dispose of defective mitochondria while stimulating healthy mitochondria to proliferate through mitochondrial biogenesis. In the process, highly functional mitochondrial subpopulations are segregated from poorly functional mitochondria, which are targeted for degradation (Piantadosi&Suliman, 2012). This process is controlled by a numerous transcription factors, such as peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), mitochondrial transcription factor A (Tfam), mitogen-activated protein kinase (MAPK) and Sirtuin-1(Sirt-1), as well as at a post-transcriptional level. The master gene of mitochondrial biogenesis is the PGC 1-αcofactor, that infact coordinates the actuation of mitochondrial biogenesis starting from several stimuli. Infact, depending on the stimulus, the program is executed through a diversity of signaling pathways that converge on a handful of co-activators and nuclear transcription factors (including PGC-1α, PGC-1β) and nuclear respiratory factors (NRF-1 and NRF-2). PGC-1 co-activators regulate, moreover, the expression of Tfam, a key factor that regulates mtDNA replication and transcription and has been found to orchestrate a wide variability of anti-inflammatory and metabolic nuclear genes; those most directly correlated to mitochondrial biogenesis in inflammation are covered here, comprising the NRF-1, NRF-2 (Cherry &Piantadosi, 2015). The PGC-1α activity is controlled at post-translational level by phosphorylation, methylation and acetylation (Wood Dos Santos et al., 2020). PGC-1α is also implicated in other functions, such as regulator of mitochondrial genome copy number, regulation of mitochondrial dynamics and modulation of oxidative phosphorylation. Moreover, these organelles are highly dynamic and undergo fusion (the joining of two organelles into one) and fission (the division of a single organelle into two. Mitochondria also undergo other dynamic activities, such as transport (directed movement within a cell) and degradation (targeted destruction via the mitophagic pathway). All these activities are essential for maintaining a healthy mitochondrial population (Moreira et al., 2017). The maintenance of mitochondrial structural integrity, biogenesis and function is indispensible to the cells, since mitochondrial dysfunction can cause disturbances in energy metabolism, intensification ROS synthesis and, consequently, trigger mechanisms of apoptotic cell death. In fact, it has been shown that reduced mitochondrial performance is a hallmark of aging probably due to the central role of mitochondria in metabolism and cellular activity. Thus, the possible toxicity of mitochondrial ROS (mtROS), originating from mitochondrial respiratory

chain, led to the creation of the oxidative stress theory of aging, which proposed that the accumulation of oxidative damage to macromolecules is a significant point in the aging process (Moreira et al., 2017). Mitochondrial biogenesis can be stimulated by exercise, fasting, cold exposure (thermogenesis), oxidative stress, and inflammatory cell stress. In view of this, a lot of strategies that intention to act on mitochondrial function are studying; an correct nutrition and a constant physical activity are indispensable and modifiable factors that play a key role in preventing and/or delaying the mitochondrial deterioration, acting on the mitochondrial biogenesis.This paper searched to summarize the impact of exercise and phytochemicals intake on mitochondrial biogenesis.

Material & methods

The source articles were identified using the online databases MEDLINE (Pubmed), Scopus and Web of Science, using keywords, including "mitochondria", "biogenesis" "physical activity", "ROS", "oxidative stress",and "phytochemicals". Relevant references were inspected and limited to peer-reviewed papers published from 2010 to 2020.

Results

Exercise influences mitochondria, which in turn influence exercise.

Beneficial effects of physical activity on mitochondrial health are well substantiated in the scientific literature: a regular exercise improves mitochondrial quality and quantity in normal healthy population, and cardio metabolic and neurodegenerative disorders and aging. However, several recent studies questioned this paradigm, suggesting that extremely heavy or exhaustive exercise fosters mitochondrial disturbances. Exercise-induced mitochondrial dysfunction (EIMD) might be a key proxy for negative outcomes of exhaustive exercise, being a pathophysiological substrate of heart abnormalities, chronic fatigue syndrome or muscle degeneration (Ostojic, 2016).

ROSs excites the mitochondrial genesis cascade in reply to endurance activity training, as in muscle shrinkage. The newly made mitochondria are recognized to be highly effective and synthetizeless ROSs for the similarquantity of formed ATP. Systematicactivity training ameliorates expression of proteins related mitochondrial genesis, as in PGC-1α, NRF-1, and Tfam(**Figure 2**). PGC-1α is asignificant transcriptional co-activator of nuclear genes encoding mitochondrial proteins, while Tfam checks the expression of mitochondrial DNA. For instance, expression of PGC-1α in skeletal muscle was considerablyincreasedsubsequentfour weeks of endurance activity training, indicating a skeletal muscle contraction-stimulated action of mitochondrial genesis. Mitochondria are not the singlecauses of ROS during muscle shrinkage. For instance, it has been revealed that muscle shrinkage enhances superoxide activity in cytosol, with a tardyintensification in mitochondria. It has been suggested that NADPH oxidases are the possiblecausesof superoxide creation. Consequently, ROS production(value of H_2O_2) was revealed to intensify in single mitochondria after severe muscle contraction in contrast with rested skeletal muscle biopsy model(Huertas et al, 2019; Mankowski et al., 2015).

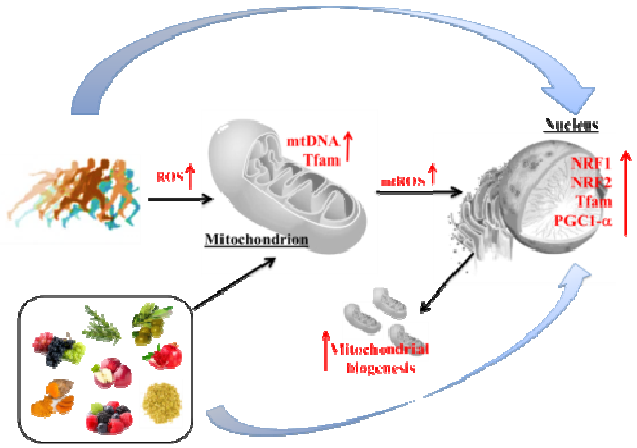

Figure 2. Mitochondrial biogenesis is influenced by exercise and nutrients.
Abbreviations. ROS: reactive oxygen species; mtROS: mitochondrial ROS; NRF1- NRF2: nuclear respiratory factors; PGC1-α: peroxisome proliferator-activated receptor-γ coactivator-1α; mtDNA: mitochondrial DNA; Tfam: mitochondrial transcription factor A.

During a physical exercise there is obviously an energy deficit with ATP reduction with an intensification in ADP and AMP on the one hand and an upsurge in NAD^+ at the expense of NADH on the other; the AMP/ATP and NAD^+/NADH ratios is the cellular sensors of energy well-being; high levels of AMP stimulates the AMP-activated protein kinase (AMPK), while high levels of NAD^+ activates the Sirt-1 enzyme; the AMPK

determines the phosphorylation of the PGC1-alpha factor while Sirt-1 determines its deacetylation; both post-translational changes (phosphorylation and deacetylation) activate PGC1-alpha which is able at this point to bind to dissimilar transcription factors such as NRF1 and NRF2, estrogen-related receptors (ERRs), peroxisome proliferator-activated receptors (PPARs), thyroid hormone receptors (THRs) which in synergy excite the expression of the entire mitochondrial gene network which translates into greater efficacy in fat burning and thermogenesis. Exercise is also capable of producing ROS during energy depletion and in a situation of hypoxia followed by hyperoxia, also signals transducers skilled of activating mitochondrial biogenesis through the AMPK pattern (Lysenko et al, 2016). Exercise also excites enzymes involved in β-oxidation, the tricarboxylic acid cycle and the electron transport system. Consequently, the oxidative capacity of skeletal muscle could increase, up to 40% in response to physical exercise. Increases in respiratory capacity appear to be explained by Co-activator of PGC-1α, it is a central, exercise-induced regulator, and its expression is stimulated by kinases that exercise, the capacity of the electron transport system an augmented expression of mitochondrial enzymes that facilitate aerobic metabolism. Furthermore, the definite alterations in the electron transport system are contingent on the intensity of the exercise. The flow of electrons and the oxidative ability seem to increase more with physical exercise and this development is independent of the training intensity (whether it is high intensity or simple strength). It is also recorded that after physical improves. This phase increases by 25%, much more in response to high intensity or simple strength (Popov et al., 2015; Cobley et al., 2015) comprise the protein MAPK and AMPK. Numerous trials have linked PGC-1α with the maintenance of muscle mass. The PGC-1α content correlates positively with oxidative ability and training status (Rius-Pérezet al., 2020).

AMPK stimulates mitochondrial biogenesis and β-oxidation by regulating PGC-1α. PGC-1α directly increases the production of NRF-1, NRF-2, and Tfam, all of which upsurge mtDNA, an indicator of mitochondrial biogenesis and mitochondrial function.Mitochondria are highly subtle to contractile substances released into the muscle after exercise, promoting biogenesis and helping to maintain cellular health. Numerous studies have described that an upsurge in mitochondrial biogenesis is obtained more with an increase in the volume of training, rather than in intensity. Complex IV, which is the electron acceptor in oxidative phosphorylation (the final phase of cellular respiration), can increase its enzymatic capacity in reducing the loss of electrons, leading to a lower synthesis of ROS Hypoxia Triggers AMPK (Mungaiet al., 2011).Although exercise-induced ROS synthesis is asignificant signaling pathway to induce biological adaptations to training, ROS over synthesis could also have a damaging impact on cells and tissues, i.e., lipid and protein peroxidation. This concern has led some experts to propose consuming more dietary antioxidants and antioxidant-containing supplements to mitigate the ROS synthesis that can cause excess oxidative stress during and after exercise(Mankowskiet al., 2015).

Mitochondrial active phytochemicals

Bioactive compounds reported to stimulate mitochondrial biogenesis are linked to many health benefits such augmented longevity, improved energy utilization, and protection from reactive oxygen species (D'Angelo, Motti, &Meccariello, 2020; D'Angelo & Rosa, 2020a; D'Angelo & Tafuri, 2020; D'Angelo &Cusano 2020a; D'Angelo &Cusano, 2020b; D'Angelo, & Madonna, 2020; D'Angelo, &Cusano, 2020c).

The use of medicines derived from herbal products is an ancient practice in scientific research. Recently, food ingredients, plant extracts, have received attention because able to generate healthy benefits(D'Angelo, 2020a; D'Angelo 2020b). Phytochemicals are plant secondary metabolites, which are synthesized to protect the plant against biotic and/or abiotic stresses. Certain herbs and dietary supplements have been reported to support augmented mitochondrial mass or number. These include an herb called *Kaempferiaparviflora* (common name black turmeric or black ginger), foods like dark chocolate (cocoa extracts), plant phytochemicals such as the proanthocyanidins, *Rosmarinusofficinalis* (rosemary; source of ursolic acid) (Bordoni&Gabbianelli, 2020; Mankowski et al., 2015). Recently acopiousness of evidence shows the promising role of polyphenolic compounds on mitochondrial structure and function. Substantial literature proposes that polyphenols play a vital role in preventing and managing several syndromes.

Polyphenols constitute one of the most numerous and ubiquitous families of plant metabolites and an integral part of both human and animal diets, ranging from simple phenolic molecules to highly polymerized compounds with molecular weights greater than 30,000 Da (D'Angelo, 2020a), and they have been classically described as antioxidants owing to their well-established ability to eliminate free radicals and ROS. Polyphenols have various biological activities (D'Angelo 2020b; D'Angelo, Martino, & Cacciapuoti, 2019; Martino et al., 2019) and in particular, they are antioxidants (Zappia et al., 2010; D'Angelo&Sammartino, 2015, Nasso et al., 2021) and they can be considered a valid nutritional support against oxidative stress caused by physical activity. In fact, to date, the effects of diverse polyphenols have been studied in a wide range of operating conditions, using a variety of integration, timing and dosage strategies (D'Angelo, 2020a; D'Angelo, & Rosa, 2020b; Malagut et al., 2013).During the last decadegrowing evidence reports the ability of polyphenols to perform several important biological activities in addition to their antioxidant activity. Special attention has been given to the ability of polyphenols to modulate mitochondrial processes (**Table 1**).

Quercetinis one of the major flavonoids of human diets, and approximately 3 to 38 mg of quercetin is consumed per day. Excellent food sources of quercetin are onions, in particular red ones, capers (it is the plant

that contains the greatest amount by weight), lovage (black mountain celery), red grapes and red wine, tea green, blueberry, apple, propolis, celery. This polyphenol has been extensively explored and that has shown to be very effective in inducing mitochondrial biogenesis. It has been reported to activate Sirt-1 and PGC-1α, and to increase the mtDNA and cytochrome C content in both skeletal muscle and brain of mice (Davis, Murphy, Carmichael, & Davis, 2009). The action of quercetin on endurance exercise and mitochondrial genesis was also considered in untrained male subjects. The researchers demonstrated that quercetin not only increased mtDNA copy quantity, but also encouraged a substantial intensification in the physical performance (Nieman et al., 2010). Comparable outcomes were also detected *in vitro*, in which quercetin processing increased the mtDNA quantity (Rayamajhi et al., 2013), and the expression value of PGC-1α, NRF-1, and Tfam in a dose-dependent manner. Quercetin not only enhanced mitochondrial membrane potential, oxygen consumption, ATP levels in mitochondria, but also augmented the mitochondrial copy number (Qiu, Luo, & Chen, 2018).Thus, both *in vivo* and*in vitro* data support the notion that quercetin induces mitochondrial biogenesis through the PGC-1α/NRF-1 and Tfam signaling (Wood Dos Santos et al., 2018; Li et al., 2016; Henagan, Lenard, Gettys, & Stewart, 2014 ; Scarpulla, 2011).

Table 1.Some effects of polyphenols on mitochondrial biogenesis.

POLYPHENOLS	FOOD	EFFECTS	REFERENCE
Epigallocatechin-3-gallate (EGCG)	Green tea 	EGCG is a promoting effector of oxidative phosphorylation and mitochondrial biogenesis in Down's syndrome cells, acting through modulation of the cAMP/PKA- and Sirt-dependent pathways	Valenti et al., 2013
Resveratrol (trans-3,5,4'-trihydroxystilbene)	Red wine 	Treatment with moderate doses of resveratrol results in AMPK activation, induction of mitochondrial biogenesis, and improved mitochondrial function	Price et al., 2012
		Resveratrol preserves mitochondrial function, stimulates mitochondrial biogenesis, and attenuates oxidative stress in regulatory T cells of mice fed a high-fat diet.	Wang et al., 2014
Hydroxytyrosol	Olives and virgin olive oil 	Hydroxytyrosol promotes mitochondrial biogenesis and mitochondrial function in 3T3-L1 adipocytes.	Hao et al., 2010
		Dietary supplementation of hydroxytyrosol may contribute to eye health by preventing the degeneration of retinal pigment epithelial cells induced by oxidative stress.	Zhu et al., 2010
		Hydroxytyrosol promoted mitochondrial biogenesis through increased mitochondrial DNA content and expression of peroxisome PGC1α, nuclear respiratory factor-1, and mitochondrial transcription factor A.	Calabriso et al., 2018
		Hydroxytyrosol enhanced mitochondrial fusion and mitochondrial complex I and II activities in muscle of excessive exercise rats.	Feng et al., 2011
Quercetin (3,3',4',5,7-pentahydroxyflavone)	Red onions  Apples 	Dietary quercetin supplementation can attenuate insulin resistance and improve skeletal muscle mitochondrial function	Henagan et al., 2014
		Dietary quercetin increased skeletal muscle PGC1α and mitochondrial number.	Davis et al., 2009
		Quercetin enhanced mitochondrial membrane potential, oxygen consumption, adenosine triphosphate levels in mitochondria, and increased the mitochondria number.	Qiu et al., 2018

Hydroxytyrosol, contained in extra virgin olive oils and in olives, is alternativephytochemicalrelatedwith mitochondrial genesis. *In vitro*experiments have described the capability of hydroxytyrosol to stimulate PGC-1α by deacetylation by Sirt-1 (Zhu et al., 2010). The intake of this polyphenolmodified the PGC-1α action in rats, as well as the expression of mitochondrial centers I and II in skeletal muscle of rats to ergometric movements. An increasedability of endurance activity in the trained subjects was also detected (Feng et al., 2011). Furthermore, in difference to inducing actionof mitochondrial genesis detectedbetweenmodestactivity experimental subjects, extreme exercise reduced the PGC-1α value. This action was completelychanged back by administration of polyphenol (Feng et al., 2011). Further, in addition to inducing PGC-1α expression, hydroxytyrosol has been shown to up-regulate NRF-1 and TFAM, increase mtDNA content, and ATP synthesis in endothelial cells (Calabriso et al., 2018; Wood Dos Santos et al., 2018; Hao et al., 2010).

Resveratrol is the most well-known polyphenolic stilbenoid, found in red wine, mulberries, rhubarb, and fruits such as blueberries, many red grape varieties, and peanuts to name a few, that plays an important role in a large variety of biological activities. Resveratrol has been observed to be effective in inducing PGC-1α action in the liver and muscle of mice by facilitating Sirt1-mediated deacetylation, which in turn activates its transcriptional action. There are indications showing that resveratrol acts primarily by activating AMPK, through the inhibition of phosphodiesterase, ATP synthase, or OXPHOS complex III (Wood Dos Santos et al., 2018;). Resveratrol induced PGC-1α and mtTFA expression to augment mitochondrial biogenesis and influence proteins expression to regulate the balance of mitochondrial fission/fusion, thus maintaining mitochondrial homeostasis (Peng et al., 2016). Studies on cultured muscle cells have revealed that treatment with resveratrol stimulates the manufacture of new mitochondria. It has also been reported that feeding resveratrol to mice

improves muscle mitochondria and consequences in increased running endurance (Wang et al., 2014; Price et al., 2012).

Epigallocatechin-3-gallate, a member of a natural polyphenol family, found in great amount in green tea leaves, can counteract oxidative stress, restore mitochondrial energy deficit and can prevent mitochondrial deterioration inducing mitochondrial biogenesis by modulating key regulators of mitochondrial metabolism (Ha et al., 2018; Valentiet al., 2013).Growing evidence has shown that apple polyphenol extracts have a radical scavenging activity, and exhibit therapeutic efficacy, including anti-tumor, anti-allergy, anti-obesity, anti-fatigue, and life-extending effects (Boccellino et al, 2020; Boccellino& D'Angelo, 2020; Vuoso et al., 2020; Vuoso et al., 2020a; D'Angelo &Ascione, 2020). The representative components of apple polyphenols are procyanidins, which are complex mixtures of the polymerized forms of (+)-catechin or (−)-epicatechin concatemers, leading to structural diversity. Procyanidins are potentially effective targets as nutraceuticals or pharmaceuticals in the prevention and treatment of oxidative stress.Apple procyanidins promote mitochondrial biogenesis and proteoglycan biosynthesis in chondrocytes (Masuda et al., 2018). Mizunoya et al. detected that the oral consumption of apple polyphenols up controlled the oxidative myosin heavy chain isoform myosin heavy chain type IIx/IIband shifted it to the oxidative fiber variety, causing the improvement of the muscle endurance ability in rats (Mizunoyaet al., 2015). Alimentary apple phytochemicalsupgraded the survival and syndrome of murine cardiomyopathy by reducing the vulnerability to ventricular arrhythmias, proposing that apple phytochemicals might encourage the mitochondrial activity (Mizunoya et al., 2015; Sunagawa et al., 2014).

Conclusions

The significance of mitochondria for both health and athletic performance highlights the prominence of better understanding the elements that control exercise-induced modifications in mitochondrial genesis. Datapropose that training powermay be asignificantfactor of enhancements in mitochondrial utility. Contrary, it seems that training volume, rather than training intensity, may be an essentialfactor of exercise-induced perfections in mitochondrial quantity. Due to the small quantity of human investigations, more study is necessary to prove the trends underlined in this manuscript, and further investigations are necessary to examine the properties of differentkinds of training on the mitochondria. The information summarized in this narrative review clearly suggests that mitochondria represent an important intracellular target of polyphenols. Currently, it is clear that part of the antioxidant properties of polyphenols might be due to their capacity to induced mitochondrial biogenesis and improve mitochondrial function, which increases the mitochondrial efficiency leading to reduction in ROS synthesis. An interesting observation is that the reactive oxygen species produced by mitochondria are important for mitochondrial quality control. However, the results of human studies aiming at finding an ergogenic or healthy effect of polyphenols are contradictory. With respect to pharmacokinetics, polyphenols in general is a low bioavailability compound if administered per *os*, with a lack in solubility in water. To ensure that high polyphenols concentrations will reach a certain target cell is not currently possible and may depend on biotechnology-related strategies that would increase phytochemicals bioavailability (**Figure 2**).

In conclusion, the notion that antioxidants are detrimental for exercise-induced benefits has already been reported in humans, although the mechanisms remain unclear. The studies demonstrating the role of polyphenols as an inducer of mitochondrial biogenesis are incipient, but serve as a base to develop new drugs that would be utilized in pathologies involving mitochondrial dysfunction.

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