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Mitochondrial Metabolism, Dysfunctions in Senescence Cell and the Possible Interventions through Herbal Medicines

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ABSTRACT

The mitochondria are the cell's powerhouse. They are considered ubiquitous organelles of all eukaryotic cells, being responsible for the cell's life and death cycle. Through stimuli in the environment in which they live, mitochondria can modulate their own biogenesis as well as signal retrograde to the nucleus to modify the structure of their proteins. Since the mitochondrial genome contains only 37 genes, much of the encoding of its proteins depends on the nuclear genome. Thus, the communication between mitochondria and the nucleus seems to be a target of science in understanding the pathologies associated with this organelle. Some medicinal herbs have been shown to influence mitochondrial biogenesis, such as Gynostemma pentaphyllum (GP) and berberine, which increase the phosphorylation of proteins AMP-activated protein kinase (AMPK). Just as GP and berberine phosphorylate AMPK in signaling for mitochondrial biogenesis, the sesquiterpene beta-caryophyllene (BCP) demonstrated positive results in reorganizing mitochondrial transcription factors, being an agonist of the peroxisome proliferator-activated alpha receptor (PPAR- α). Another plant derivative, the non-psychoactive cannabinoid known as cannabidiol (CBD), has been showing control in the metabolism of calcium in the mitochondrial matrix. In this review, we seek to get a closer look at the biochemical mechanisms of action of some of these plants, as well as their synergies in the results of different treatments. In the view of oriental medicines, the use of associated medicinal herbs has always been part of their treatment protocols. However, the effectiveness of these treatments in relation to plant synergy can be observed in future clinical trials for better understanding.

Keywords: Mitochondrial Biogenesis; Cell Senescence; Retrograde Signaling; Medicinal Herbs

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Introduction

Mitochondria are considered ubiquitous organelles in eukaryotic cells, where they are essential for the life cycle and cell death [1]. Its structure is formed by two membranes, an internal membrane permeable to ions and an external membrane permeable to factors <5 kDa [2]. In this structure, mainly in the mitochondrial matrix, adenosine triphosphate (ATP) is generated by oxidative phosphorylation (OXPHOS). An electrochemical gradient across the inner membrane leads to a proton driving force in the intermembrane space that triggers ATP synthesis [3]. This process occurs due to electrons donated from reduced forms of nicotinamide adenine dinucleotide (NADH) and

flavin adenine dinucleotide (FADH₂) generated by the oxidation of acetyl-CoA in the tricarboxylic acid (TCA) cycle [4]. Under normal conditions, the oxidation of certain energy substrates, especially fatty acid and glucose-pyruvate, generates acetyl CoA in the mitochondrial matrix [4]. Electrons from NADH and FADH are transferred through the electron transport chain (ETC) components in the inner mitochondrial membrane. The transfer of electrons along the ETC induces the flow of protons through the inner membrane reaching the intermembrane space. Upon returning to the mitochondrial matrix, the protons trigger an enzyme also known as ATP synthase, which makes it possible to synthesize ATP (Fig 1) [5].

Figure 1

Mitochondrial biogenesis

Mitochondrial biogenesis is a highly complex process [6]. For a better understanding of how this whole process works, it is necessary to first examine the gene transcription factors involved in this mechanism [7].

Bearing in mind that the control of activation or deactivation of genes comes from signals originating from the environment in which cells

live, such as food intake, thought processing, sensitivity to temperature and light intensity, the process of signaling mitochondrial biogenesis is no different [8]. Upon receiving stimuli such as cold and fasting, a protein cAMP response element-binding protein (CREB) is phosphorylated through another signaling protein, protein kinase A (PKA) [9,10]. Once phosphorylated, the CREB protein will continue the transcription process by phosphorylating the

peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1 α) (Fig. 2) [11]. Likewise, there is another metabolic route that occurs through physical exercise, where calcium binds to two proteins, calmodulin-dependent protein kinase IV (CaMKIV) and calcineurin A (CnA), which can activate phosphorylation of CREB protein, and, consequently, promote signaling for peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1 α) transcription [12]. Once the expression of PGC-1 α is increased, there is a sequence for the transcription of specific proteins that interact in the process, not only of protein synthesis of the respiratory chain, but also of the replication of this organelle, among them myocyte enhancement factor 2 (MEF-2) [13], nuclear respiratory factor 1 and 2 (NRF-1 and NRF-2) [14], the estrogen-related alpha receptor (EER- α) [15], and also the receptors activated by the peroxisome proliferator-activated receptor alpha (PPAR- α) [16], the latter being responsible for the formation of proteins that carry out beta oxidation in mitochondria. A curious fact that deserves attention is that MEF-2, like CREB, interacts in the PGC-1 α transcription process [11]. Subsequently, MEF-2 is activated by PGC-1 α itself, where it will be transferred into the mitochondria, triggering the transcription of cytochrome c oxidase (Fig. 2) [17]. This path is not yet well known to its full extent, but it seems that there is a loop between the process in activating the transcription of both.

Another no less important factor about PGC-1 α signaling is the activation of the AMP-activated protein kinase (AMPK) (Fig. 2) [18]. This protein is highly expressed in catabolic processes, such as physical activity [19]. As a result of a power outage, AMPK is strongly phosphorylated, increasing its signaling to PGC-1 α [20]. Thus, the other signaling proteins of the mitochondrial

biogenesis mentioned above initiate a biochemical cascade not only for protein synthesis but also for the replication of the mitochondrial genome itself, mainly related to the respiratory chain [7]. There is also a transcription protein synthesized in the cytoplasm of cells, called mitochondrial transcription factor (TFAM), which plays a fundamental role in the maintenance of mitochondrial proteins, both in transcription and in the replication of this organelle [21]. However, not only do these factors interact in maintaining the health of mitochondria, but their own genome also has a strong interaction for the preservation of their structures [22].

Mitochondrial genome

The mitochondrial genome, unlike the nuclear genome, is circular and has 16,569 DNA base pairs, whereas the nuclear genome contains 3.3 billion DNA base pairs [22,23]. The mitochondrial genome is made up of only 37 genes [23]. However, in each protein in the respiratory chain, there is bilateral participation between the nuclear genome together with the mitochondrial genome (Fig. 3) [24]. For example, in complex I of the respiratory chain, where the entire electron flow process begins, 39 genes come from the nucleus with only seven coming from mitochondria [25]. In complex II, the four genes come exclusively from the nucleus, with no involvement of the mitochondrial genome in this protein [26]. In complex III, ten are nuclear and only one mitochondrial [27]. In complex IV, we have ten nuclear and three mitochondrial cells [28]. In complex V, we have 14 nuclear and two mitochondrial [28]. Researchers also claim that mitochondrial DNA (mtDNA) is inherited exclusively from the female [29]. This is due to the presence of mitochondria in the cytoplasm of the egg when they are assigned to the zygote, or unicellular embryo [30]. In the case of sperm,

mitochondria end up being eliminated by process of ubiquitination as soon as it enters the egg [31]. Once fertilized, this cell will replicate mitochondrial DNA only from the mother [29]. However, despite the rarity, there have been

scientific reports of paternal mitochondrial inheritance in humans [32]. This fact is due to a genetic mutation in the maternal mitochondrial DNA itself, which makes it possible to inherit the paternal mitochondrial genome [33].

Figure 2

CaMKIV, Calcium/calmodulin-dependent protein kinase IV; **CREB**, cAMP response element-binding protein; **AMPK**, Adenosine monophosphate kinase; **PGC-1α**, Peroxisome proliferator-activated receptor-gamma coactivator-1alpha; **MIF-2**, myocyte enhancer factor-2; **NRF-1**, Nuclear respiratory factor 1; **PPAR-α**, Peroxisome proliferator-activated receptor alpha; **ERR-α**, Estrogen-related receptor alpha; **TFAM**, Transcription Factor A, Mitochondrial.

Figure 3

Mitochondria and Senescent Cells

Cellular senescence is increasingly recognized as the main cause of health loss and physical conditioning associated with aging [34]. The amount of dysfunctional mitochondria in senescent cells is a reality that has been reported in several scientific studies, and its inefficiency of OXPHO and the increase in reactive oxygen species (ROS) trigger serious

damage to cells [35]. Mitochondrial enzymes need to be in perfect working order to synthesize ATP in the ideal amounts for cell functioning [36]. Any enzymatic change linked to the production of energy in these organelles can seriously compromise the functioning of tissues [37]. When mitochondria are not working well, a wide variety of symptoms can arise, including delay or regression in physical and mental development

[38], impaired language [39], impaired social interaction [40], intellectual disability [38,40], neuropsychiatric symptoms (ADHD, anxiety, OCD, depression) [41], seizures [40], headaches [42], hearing problems [40,43], weakness [42], short stature [38,42], fatigue [44,45], gastrointestinal symptoms [40], endocrine disorders [46], and many others. More and more research now suggest that mitochondrial dys- function can

have a major and important influence on several health conditions, such as autism [47, 48], bipolar disorder [49], schizophrenia [49], depression [50], cancer [51, 52], diabetes [53], Parkinson's disease [54], asthma [55], chronic fatigue syndrome [44,45], Alzheimer's disease [56], gastrointestinal disorders [40], nonalcoholic fat liver disease [57] and several others.

Table 1

S. no.	Disease	Mitochondrial changes	Reference
1	<u>Autism</u>	↑ROS ↓NADH oxidase activity	<u>Giulivi et al. (2010)</u>
2	<u>Bipolar disorder and schizophrenia</u>	↓ mt Respiration ↑ mtDNA mutation	<u>Clay et al. (2011)</u>
3	<u>Depression</u>	Alteration of OXPHOS ↑ROS	<u>Allen et al. (2018)</u>
4	<u>Cancer</u>	mtDNA mutations	<u>Wallace (2012)</u>
5	<u>Diabetes</u>	↓ATP Production ↑ROS	<u>Sivitz & Yorek (2009)</u>
6	<u>Parkinson's disease</u>	Complex I deficiency	<u>Chen et al. (2019)</u>
7	<u>Asthma</u>	mtDNA alteration ↑ROS	<u>Reddy (2012)</u>
8	<u>Chronic Fatigue Syndrome</u>	↓ATP Production	<u>Myhill et al. (2009)</u>
9	<u>Alzheimer's disease</u>	mtDNA oxidation/mutations ↑ROS	<u>Cenini & Voos (2019)</u>
10	<u>Fat Liver</u>	Depletion of mtDNA ↓OXPHOS ↑β-oxidation	<u>Wey et al. (2008)</u>

In a study on mitochondria in senescent cells, the authors Korolchuk et al (2017) demonstrated that cell senescence is increasingly recognized as the main contributor to health loss and especially in decreasing physical conditioning associated with aging [58]. Furthermore, it has been shown that senescent cells accumulate dysfunctional mitochondria, mainly in the metabolism of oxidative phosphorylation, leading to high production of reactive oxygen species [58]. Because cell senescence is part of a range of cellular responses to extrinsic and / or intrinsic harmful processes that affect homeostasis, especially the integrity of both the genome and the proteome [59], studies have suggested that unregulated mitochondrial fusion, fission and mitophagies have been observed in

cell senescence. These studies have shown that, in senescent cells, mitochondrial dynamics are strongly reduced [60]. Stress-induced premature senescence showed elongated mitochondria, with increased crest structure, as well as increased mitochondrial content [61]. Although studies are already well documented about mutations in mtDNA as a cause of different types of mitochondrial diseases [62], the impact of this mutation as a senescence factor has not been well investigated [63]. In the past, the first studies excluded the presence of deletions or single base changes in mtDNA [64]. However, more recently it was demonstrated in cell cultures that mtDNA depletion exhibited senescent phenotypes, characterizing the potential involvement of mtDNA damage in cell

senescence ^[65]. In fact, recent studies support the idea that all the nucleus-derived transcription factors mentioned above that govern mitochondrial biogenesis, PGC-1 α , NRF-1/2, sirtuins and TFAM are somehow involved in cell senescence ^[63] (**Fig 2**).

Retrograde Signaling in Mitochondrial Dysfunction

In mammalian cells, retrograde mitochondrial signaling is well understood by the scientific community. This process occurs due to an altered nuclear expression in response to mitochondrial dysfunction with a series of signaling pathways involved in this communication ^[66]. From studies on metabolic diseases, inflammation and cancer, we have an extensive list of important small molecules participating in retrograde mitochondrial signaling, including ROS, NAD⁺ / NADH ratio, Acetyl-CoA, ATP, Ca²⁺, and oncometabolite ^[67]. Enzymes such as calcineurin, protein kinase-C (PKC), CaMKIV, c-Jun N-terminal kinases (JNK) and mitogen activated protein kinase (MAPK), as well as the transcription factors activating transcription factor 2 (ATF2), CCAAT/enhancer-binding protein- δ (C/EBP- δ), nuclear factor of activated T cells (NFAT), CREB, early growth response protein 1 (Egr-1), C/EBP homologous protein (CHOP) and nuclear factor kappa-beta (NF- κ B) participate in the retrograde mitochondrial signaling of mammals ^[68] (**Fig. 4**). Research has reported that, depending on cell type and cell conditions, there are essentially two branches in the Ca²⁺ mediated retrograde signaling pathway: 1. Ca²⁺ mediated retrograde signaling / calcineurin for nuclear translocation of transcription factors, NF- κ B, NFAT, CREB and heterogeneous nuclear ribonucleoprotein A2 (HnRNPA2); and, 2. Direct activation of Ca²⁺ dependent protein kinases, such as those previously mentioned, PKC, JNK, MAPK and

CaMKIV ^[67]. The activation of these signaling pathways in epithelial cells converges in the positive regulation of genes that affect several cellular functions, including resistance to apoptosis and resistance to multiple drugs ^[69]. On the other hand, retrograde signaling is triggered by a mitochondrial signal, which, in turn, is relayed to one or more protein molecules that reach the nucleus. Oncometabolites, for example, are metabolites whose abundance is significantly increased in cancer cells compared to normal cells ^[70]. Increasing evidence shows that oncometabolite and retrograde signaling contributes to cancer progression ^[67,70]. Research has already shown the retrograde signaling involved in epigenetic changes and post-translational protein modifications, including proto oncogene c-Src, MAPK, AMPK, poly (ADP ribose) polymerase (PARP) and sirtuin 1 (SIRT1) in various pathological conditions ^[68, 71, 72].

Medicinal Herbs

The plant kingdom has adapted to all habitable environments on planet Earth. Because they are inanimate beings, the challenges related to environmental stress caused several species of plants to develop many molecules to avoid animal attacks and other environmental aggressions ^[73]. These molecules synthesized by plants give the ability to exhale fragrances, colors and even toxicity as a protective mechanism. ^[74] Apparently, the discovery of medicinal plants by the first humans may have been an exercise in trial and error due to the need to relieve the manifestations of symptoms, such as pain, inflammation and allergic reactions to insect bites ^[75]. In the beginning, before the advent of writing, this knowledge was transmitted from generation to generation through word of mouth. Later, many plants were registered as having medicinal properties and

were used to treat many diseases [76]. Several natural products from plants and animals have been the source of medicines, especially for anticancer and antimicrobial agents [77, 78]. Throughout history, especially in the 20th century, traditional medicine has been overshadowed by modern medicine as a means of treatment for human diseases [79]. However,

in recent decades, the increase in the use of medicinal plants in the treatment of diseases has shown remarkable results in many countries, including developed countries such as the United Kingdom, Germany, France and others [80, 81, 82]. In fact, many extracts of medicinal plants are being used as prescription drugs with promising results in several pathologies [83].

Figure 4

$m\Delta\Psi$, Mitochondrial membrane potential; **PKC**, Protein Kinase C; **CaMKIV**, Calcium/calmodulin-dependent protein kinase IV; **JNK**, c-Jun N-terminal kinases; **MAPK**, mitogen-activated protein kinase; **ATF2**, Activating Transcription Factor 2; **CREB**, cAMP response element-binding protein; **Egr-1**, Early growth response protein 1; **CEBP-δ**, CCAAT/enhancer-binding protein delta; **CHOP**, C/EBP homologous; **NFAT**, Nuclear factor of activated T-cells protein; **NF-κβ**, Nuclear factor kappa-Beta.

Beta-caryophyllene (BCP), for example, is a sesquiterpene found in several types of plants, mainly in *Cannabis Sativa* [84]. This resin has remarkable anti-inflammatory properties, as well as antitumor activity, including the induction of apoptosis by inhibiting B-cell lymphoma 2 (Bcl-2) activity [85]. BCP also features the ability to

rearrange the mitochondrial transcription factors, suffering retrograde signaling in this type of pathology [86]. Thus, the BCP works as a peroxisome proliferator-activated receptor alpha (PPAR-α) agonist, one of the most important transcription factors in mitochondrial biogenesis [87]. Intriguingly, PPAR-α is predominantly

present in many cells, including in the liver. Previous studies have demonstrated that PPAR- α plays a critical role in the modulation of energy balance and regulation of hepatic lipid through mitochondrial metabolism [88]. Another mechanism of inflammatory protection exerted by BCP is to restore antioxidant enzymes in mitochondria, mainly superoxide dismutase (SOD), and inhibited lipid peroxidation as well as glutathione (GSH) depletion in neurons [89].

Similar to the mechanisms of action of BCP, beta-caryophyllene oxide (BCPO), due to its high biological activity, was extensively studied in recent years [90]. Either as a pure substance or a component of plant essential oils, BCPO was found to exhibit anti-inflammatory, antioxidant, antiviral, anticarcinogenic, and analgesic properties even better than BCP, mainly in anticarcinogenic activity [90, 91]. BCPO induced increased ROS generation from mitochondria, which is associated with the induction of apoptosis as characterized by positive Annexin V binding and TUNEL staining, loss of mitochondrial membrane potential, the release of cytochrome c, activation of caspase-3, and cleavage of PARP (Poly (ADP-ribose) polymerase) [92]. Proapoptotic activity of BCPO in cancer cells can be associated with reduced activation of NF - κ B [90]. NF - κ B regulates the expression of many genes involved in cellular proliferation, apoptosis, and inflammation (e.g., TRAF—TNF receptor - associated factor, c - FLIP—cellular FLICE - like inhibitory protein, surviving, various chemokines, and cytokines) [93]. Studies reported BCPO - induced inhibition of the constitutive and inducible NF - κ B activities in cancer cells. Moreover, they found that BCPO increased the tumor necrosis factor α (TNF- α) and caused apoptosis by inhibiting the NF - κ B activation [94].

Another plant that exerts antitumor activity associated with mitochondrial metabolism is *Artemisia annua* [95]. *Artemisia annua* has been described for over two thousand years in Traditional Chinese Medicine due to its fever-reducing capability [96]. In tumor cell artemisinin induce apoptosis by increasing metabolism, elevated concentration of iron and transferrin, and consequently increasing ROS [97]. Studies suggested that low doses of artesunate, a derivate of *Artemisia annua*, induced oncosis-like cell death, characterized by cytoplasmic swelling and vacuolization, disorganized mitochondria, dilation of the nuclei, and cell lysis [98]. However, one of the most tested hypotheses about artemisinin, another derivate of *Artemisia annua*, is that the endoperoxide bridge of the artemisinin structure reacts with either heme groups or intracellular iron, hence producing cytotoxic radicals with an alkylating capacity [99, 100, 101]. The importance of iron in mitochondrial function is well known. However, the role of mitochondrial iron trafficking in the regulation of cellular iron homeostasis is not well understood [102]. In mitochondria, iron is used for the synthesis of heme and the generation of iron-sulfur [99]. Thus, linking artemisinin to transport into the mitochondria matrix is an interesting path [103]. Once inside the mitochondria, artemisinin has greater contact with iron, pulling an electron from that metal in its endoperoxide portion, causing the formation of ROS and consequently ferroptosis [104]. Still in relation to mitochondrial metabolism, studies related that apoptosis of human umbilical vein endothelial cells (HUVEC) by artesunate and artemisinin is associated with negative regulation of Bcl-2 and positive regulation of BAX (protein X associated with Bcl-2), the genes associated with the control of apoptosis in the external mitochondrial membrane [105, 106].

As apoptosis depends on the metabolism of calcium, cannabidiol (CBD), present in *Cannabis sativa*, exerts an important mechanism on the balance of mitochondrial calcium in the mechanism of control of apoptosis ^[107, 108]. CBD is a non-psychoactive plant cannabinoid that inhibits cell proliferation and induces cell death of breast cancer cells ^[109]. Studies have shown that CBD-mediated cytosolic elevation of free Ca^{2+} has been observed in several cells, cancerous and non-cancerous ^[110], and its presence defines the scenarios of cell destiny, survival or death ^[111]. Elevated intramitochondrial Ca^{2+} is a prerequisite for the formation of mitochondrial permeability transition pore (PTP20), and consequently, apoptosis ^[112]. Usually, the increase in intramitochondrial Ca^{2+} is triggered by an increase in cytosolic Ca^{2+} . In most cases, the source of Ca^{2+} can be via the endoplasmic reticulum (ER), whose membrane is very close to the external mitochondrial membrane (OMM), facilitating the transposition of Ca^{2+} ^[113]. Thus, CBD interacts directly with mitochondrial calcium. Its effect does not depend on cannabinoid receptors or Ca^{2+} permeable channels in the plasma membrane. Instead, CBD targets the mitochondria directly by altering Ca^{2+} metabolism ^[109]. In lethal concentrations, CBD causes Ca^{2+} mitochondrial overload, the formation of stable mitochondrial transition pores and cell death ^[114]. Studies have suggested that CBD is an attractive candidate to be included in chemotherapy protocols for the treatment of acute lymphoblastic leukemia of T lineage (T ALL) for its proapoptotic activity in these cell types ^[109].

As we can see, mitochondrial metabolism is associated with numerous pathologies. Thus, controlling mitochondrial biogenesis seems to be a promising path for the treatment of several

diseases ^[115], mainly when medicinal herbs manage to activate the signals of the transcription factors involved in mitochondrial biogenesis, as in the case of berberine and jayagulan (*Gynostemma Pentaphyllum*) ^[116, 117].

Berberine is a natural isoquinoline alkaloid derived from the traditional medicinal plant *Coptis chinensis* that has numerous pharmacological properties, including antimicrobial, antioxidant, anti-inflammatory, antidiarrheal, antidiabetic, antilipidemic and antitumor activities ^[116]. Studies have shown beneficial effects of berberine in the treatment of insulin sensitivity and glucose tolerance due to berberine's ability to activate AMPK and suppress gluconeogenesis ^[118, 119]. Berberine can also activate SIRT1, a protein that has a two-way pathway in regulating AMPK ^[120, 121, 122]. In other words, SIRT1 can be regulated by AMPK as well as regulating AMPK activity. Thus, berberine has been shown to be effective both in increasing mitochondrial biogenesis and in mitochondrial function in muscle tissue of obese rats ^[120].

Following a metabolic pathway like berberine, studies have reported that *Gynostemma pentaphyllum* (GP) has also shown remarkable properties in AMPK phosphorylation ^[117]. Since AMPK is a key sensor and regulator of glucose, lipid and energy metabolism ^[121], its activation by GP improves metabolic abnormalities associated with metabolic diseases, including obesity and type 2 diabetes ^[123]. Studies have found that GP contains two saponins, also known as damulins, which activate AMPK strongly ^[117]. These damulins also act positively in the metabolism of β -oxidation and in the uptake of glucose by increasing the translocation of GluT4 to the plasma membrane in L6 myotubular cells ^[117]. A study comparing the effect of GP with a control diet and a high-fat diet showed that GP

significantly increased SIRT1 mRNA expression, as well as AMPK phosphorylation when compared to both control groups, and especially to the high fat intake group ^[123]. Several other studies have reported that GP can bring promising results in the control of metabolic syndrome by improving the function of mitochondrial metabolism and SIRT1 expression ^[124, 125, 126].

Interestingly, SIRT1 is an epigenetic enzyme involved in protein deacetylation that acts mainly as a metabolic sensor responding to changes in the energy state, deacetylation of transcription factors and crucial cofactors in cellular metabolism ^[127]. This enzyme also regulates several biological functions, including biogenesis, inflammation, apoptosis, oxidative stress, mitochondrial function and cellular senescence ^[128]. Several studies have shown that resveratrol has a good impact on SIRT1 ^[129, 130]. Resveratrol is a naturally occurring polyphenolic component that belongs to the class of stilbenes present in more than 70 species of plants, mainly in the skin of red grapes ^[131]. Studies have shown that resveratrol has inhibitory effects on various types of cancer cell lines and preclinical animal models in many types of cancer, such as colon, breast and lymphoma, due to its activity on several subcellular targets, including SIRT1 ^[132]. In fact, resveratrol uses several strategies to stimulate apoptosis in cancer therapy. One of them is to increase the level of mitochondrial oxidative stress, which, in turn, releases cytochrome C in the cytosol, activating the caspases and triggering apoptosis ^[133]. It was observed that the administration of resveratrol triggered a mitochondrial dysfunction due to the loss of the mitochondrial membrane potential, resulting in the induction of apoptosis in tumor cells ^[134]. Since most cancer cells prefer to use glycolysis to generate ATP and simultaneously

increase their glucose uptake (Warburg effect), the antitumor activity shown by resveratrol caused, at the same time, a reduction in glucose metabolism in cancer cells, as well as the induction of mitochondrial breathing in cancer therapy ^[135, 136, 137]. As mentioned

above, there is a bidirectional interaction between the SIRT1 pathway and the AMPK. Therefore, it has been reported that the SIRT1 / AMPK axis is important in the mitochondrial biogenesis, fission, fusion and mitophagy of this organelle ^[138], and resveratrol administration had antitumor impacts by affecting mitochondrial breathing through positive regulation of SIRT1 ^[139].

Discussion

Mitochondria are increasingly in evidence in the focus of treatment of various diseases. It is so important for cells that recently studies have tried to understand the transit of this organelle in extracellular spaces. In March 2020, Dache et al. published an article with surprised researchers since intact mitochondria was found in the extracellular space ^[140]. While several other studies have reported the existence of extracellular mitochondria under specific conditions resulting in platelet activation or encapsulated in microvesicles, the authors Dache et al. (2020) stated that it is remarkable how the presence of mitochondria free of intact cells went unnoticed in the normal physiological state. Studies have pointed out that intact mitochondria free of circulating cells have crucial biological and physiological roles, as it was scientific knowledge that mitochondria function as systemic messengers in cell-cell communication through the transfer of hereditary and non-hereditary constituents ^[140, 141]. Previous studies also have already reported that mitochondria translocate from one cell to another. These studies demonstrated that the

intercellular mitochondria traffic occurred both in vitro and in vivo, and in both physiological and pathophysiological conditions, including tissue damage and cancer [142, 143].

In either of these processes, a transit of mitochondria between cells was observed. Patel et al. (2017) also demonstrated that mitochondria could be internalized by different

types of cells, such as, for example, macropinocytosis, which is a specific endocytic pathway for large vesicles [144]. However, although clinical mitochondrial transplants between cells are an active area of research, the specific mechanisms and critical factors involved in the natural transfer of mitochondria between donor cells and recipient cells have yet to be fully characterized [145].

Table 2

S. no.	Herbs	Mitochondrial Interaction	Reference
1	Beta-caryophyllene	↓Bcl-2 ↑BAX (pro apoptosis cancer cell) PPAR-α (mitochondrial biogenesis)	Legaut & Pichet (2007) Yussef et al. (2019)
2	Beta-caryophyllene oxide	↑TNF-α ↓NF-κβ (pro apoptosis cancer cell)	Kim et al. (2014)
3	Artemisia annua	↓Bcl-2 ↑BAX (ferroptose cancer cell)	Li et al. (2013)
4	Cannabidiol	Ca ²⁺ PTP20 (apoptosis)	Giorgio et al. (2018)
5	Berberine	AMPK (mitochondrial biogenesis)	Teodoro et al. (2013)
6	Gynostemma pentaphyllum	AMPK (mitochondrial biogenesis)	Gauhar et al. (2012)
7	Resveratrol	SIRT1 (mitochondrial biogenesis)	Buhrmann et al. (2019)

Numerous studies have been looking for therapies on how to preserve mitochondrial structures, especially in mtDNA, with the administration of drugs, herbal medicines and nutraceutical products [125, 139]. In both cases, such as importing healthy mitochondria into dysfunctional tissues, as well as administering phytochemicals to rescue the integrity of the mitochondria in dysfunctional tissue, research has shown to be increasingly favorable to the treatment of mitochondria in relation to associated diseases. The many herbs reported in this present study had medicinal properties

aimed directly and/or indirectly at mitochondria in various diseases. This makes us reflect on how influential mitochondria are in diseases as well as in aging. Another hypothesis that could be answered in future clinical trials would be how much the retrograde mitochondrial signaling would be related to the cause of diseases such as cancer, for example. What science has known until now is that the membrane morphology of these organelles undergoes radical changes in diseases such as Alzheimer's disease, Parkinson's, non-alcoholic liver cirrhosis and cancer itself [146]. Rescuing the

anterograde signals, that is, from the nucleus to the mitochondria under normal conditions, could be a hypothesis to help reverse diseases associated with mitochondria. Once retrograde signaling is activated because of chronic stress, altering the expressions of certain genes that would modify mitochondrial structures is a fact. Administering herbal medicines and specific coenzymes that act in the respiratory chain seems to be an interesting way of controlling oxidative stress and reversing retrograde signaling processes [86, 110, 115, 116, 117, 134].

Another factor to be observed would be a possible administration of plants synergistically in the control of mitochondrial apoptosis. For example, piperlungumine, the biologically active compound from the *Piper longum* plant, when it is administered, a reduction in reduced glutathione levels is observed in cancer cells by inhibiting the enzyme glutathione reductase (GR) [147]. This would be fantastic if this type of cell did not defend itself by increasing the expression of nuclear factor erythroid 2-related factor 2 (Nfr-2). With the increase in Nfr-2, cancer cells can produce more antioxidants counterbalancing the reduction of glutathione by piperlungumin protect itself [148, 149]. However, the use of luteolin, a flavonoid found in several plants, can inhibit of Nfr-2 activity in cancer cells [150]. Therefore, the effects of piperlungumine in controlling mitochondrial glutathione levels are likely to be a promising path in herbal therapies when used in synergy with another herb such as luteolin. In the same way that drugs must be administered together to treat certain diseases, medicinal plants also follow the same reasoning.

Conclusion

Pathologies directly or indirectly related to mitochondria have been the target of studies in several types of diseases. Since enzymatic changes in mitochondrial metabolism, as well as

changes in the genome of this organelle are decisive factors in disease control, the scientific community is increasingly committed to understanding not only the functioning of mitochondria but mainly why this imbalance in its metabolism occurs in diseases. A classic example of this is the retrograde signaling between the mitochondria and the cell nucleus, as related above. Likewise, changes both environmental and emotional, as well as inadequate food intake, can cause a series of changes in the structures of mitochondria, especially in the transcription factors that modulate mitochondrial genome. Therefore, understanding how to control mitochondrial imbalance in the fight against pathologies is a necessary tool to be applied, especially when we talk about medicinal herbs which have the capacity to control the proteins involved in mitochondrial biogenesis (AMPK, PPARs e etc.). However, future studies will be needed to evaluate the results of medicinal herbs, especially when they are administered concomitantly, as well as in Traditional Chinese Medicine and Ayurvedic Medicine, and not just alone. Some studies have already shown that the synergy between medicinal herbs can really bring benefits in different treatments, but no clinical study has yet been proposed to treat mitochondrial diseases to date. As mitochondrial changes are extensive in several diseases, the proposal to administer different medicinal herbs that act in different areas of mitochondrial metabolism seems to be an interesting path from the biochemical point of view to be investigated.

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