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Review

Mitochondria-targeted natural products with potential for the treatment of mitochondria-related diseases

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ABSTRACT

Mitochondria are indispensable organelles that serve as the powerhouses of cells, playing a crucial role in maintaining cellular energy homeostasis. Consequently, mitochondrial dysfunction is recognized as a key pathogenic factor in a wide range of common diseases, including cardiovascular diseases, neurodegenerative disorders, metabolic syndromes and cancers. Due to their multitarget properties and favorable safety profiles, natural products have shown significant potential for regulating key mitochondrial biological processes, including mitobiogenesis, mitophagy, mitochondrial dynamics (fusion and fission), oxidative phosphorylation, and mitochondria-mediated apoptosis. Therefore, they have become an important resource for mitochondria-targeted therapy. Despite significant progress in mechanistic studies *in vitro*, translating these findings into clinical applications remains a major challenge. This translational gap is primarily due to unfavorable pharmaceutical properties, such as low bioavailability, poor targeted delivery, and rapid metabolic clearance. Additionally, the precise mechanisms governing mitochondria remain to be fully elucidated. In this review, we systematically summarize the specific mitochondrial pathological phenotypes in various diseases and provide a comprehensive overview of natural products that correspond to these phenotypes, along with their mechanisms of action. We also analyze common challenges associated with the absorption, distribution, metabolism, and excretion of these products. By bridging the gap between basic research and clinical application, this review aims to accelerate the development of novel therapeutic strategies for mitochondria-related diseases.

1. Introduction

Mitochondria function as the "energy factories" of cells and are essential organelles for maintaining cellular homeostasis. They possess a double-membrane system composed of the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM). The lipid-rich OMM contains transport proteins, including the β-barrel voltage-dependent anion channel (VDAC), which facilitates metabolite exchange between mitochondria and the cytoplasm [1]. The OMM also contains proteins involved in mitochondrial dynamics, such as mitofusin 1/2 (MFN1/2), mitochondrial fission factor (MFF), fission protein 1 (Fis1), and mitochondrial dynamics proteins 49 and 51 (MiD49 and MiD51) [2]. The IMM forms "cristae" that primarily contain oxidative phosphorylation (OXPHOS) complexes and optic atrophy 1 (OPA1) [2].

The primary function of mitochondria is to regulate energy metabolism by converting nutrients into adenosine triphosphate (ATP) through OXPHOS. To counteract cell damage, cells use a mitochondrial quality control system that regulates mitobiogenesis, mitophagy, and mitochondrial dynamics (fusion and fission). This system maintains the stability of mitochondrial morphology, quantity, and quality, preserving the integrity of their structure and function [3]. Mitochondria also serve as critical nodes in the calcium ion (Ca^{2+}) signaling network. Under physiological conditions, mitochondrial Ca^{2+} uptake drives bioenergetics; however, in a damaged state, mitochondrial Ca^{2+} overload triggers the opening of mitochondrial permeability transition pores (mPTP) [4, 5]. At the same time, the pro-apoptotic proteins Bax and Bak are activated, inducing mitochondrial outer membrane permeabilization (MOMP), which promotes the release of cytochrome C (Cyt-c) and ultimately leads to apoptosis [6].

Mitochondrial dysfunction can cause diseases, including neurodegenerative, metabolic, and cardiovascular diseases (CVDs) [7]. A deeper understanding of mitochondria could reveal new therapeutic targets and clarify the pathophysiological mechanisms of these diseases, enabling the development of innovative

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treatments. Because of their pleiotropic effects and favorable safety profiles, natural products have significant potential as mitochondrial regulators. However, due to limitations such as poor pharmacokinetics, a substantial gap remains between the development of natural products and their clinical application. This review outlines mitochondrial pathophysiological mechanisms underlying diseases and introduces potential natural products for mitochondrial disorders. It also analyzes their pharmacokinetic challenges and proposes strategies to improve their clinical translation.

2. Diseases associated with mitochondria

2.1. Diseases associated with impaired mitobiogenesis

Mitobiogenesis is the process by which cells increase their mitochondrial mass in response to energy demands triggered by cellular stress or environmental stimuli [8]. Peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) is the central factor in mitobiogenesis [8]. Mitochondria efficiently uptake Ca^{2+} from the cytoplasm and endoplasmic reticulum (ER), activating Ca^{2+}/calmodulin-dependent protein kinase kinase β (CAMKKβ). CAMKKβ phosphorylates and activates AMP-activated protein kinase (AMPK), which regulates the expression of PGC-1α [9]. AMPK also stimulates silent information regulator 1 (SIRT1) by increasing NAD^+ levels, leading to deacetylation of PGC-1α and forkhead box O1/O3a (FOXO1/O3a) [8, 9]. Nuclear respiratory factors 1/2 (Nrf1/2) are transcription factors downstream of PGC-1α. The expression of genes involved in mitochondrial DNA (mtDNA) regulation, such as mitochondrial transcription factor A (*TFAM*), is regulated at the mRNA level [8]. High-temperature requirement protein A2 (HtrA2/Omi)/glycogen synthase kinase-3β (GSK-3β)/PGC-1α and the PPARγ/Akt/PGC-1α signaling pathway are also involved in mitobiogenesis [10, 11]. Furthermore, estrogen-related receptor α (ERRα) is a key transcription factor required for PGC-1α-dependent gene expression [11].

Mitobiogenesis requires coordination between nuclear DNA and mtDNA. mtDNA consists of a heavy and a light strand. Initiation of human mtDNA replication at the origin of the heavy strand involves the POLγ complex with TWINKLE helicase and mitochondrial single-stranded DNA-binding protein. L-strand synthesis subsequently occurs at the origin of the light strand *via* a stem-loop structure. Replication terminates with topoisomerase IIIα, which resolves the hemicatenane formed near the origin of the heavy strand [12]. Mutations affecting replication factors result in mtDNA depletion. *TWINK* and *POLG* encode TWINKLE and POLγ, respectively. Mutations in *TWINK* and *POLG* cause autosomal dominant and/or recessive progressive external ophthalmoplegia (ad/arPEO) and Navajo neurohepatopathy [13]. The disease spectrum associated with *POLG* mutations is extensive, including myocerebrohepatopathy spectrum (MCHS) and ataxia neuropathy spectrum (ANS) disorders [14]. Deoxyguanosine kinase (DGUOK) provides guanosine and adenosine nucleotides for mtDNA replication, while thymine kinase 2 (TK2) phosphorylates pyrimidine nucleosides. Diseases caused by *TK2* mutations are mainly progressive myopathies, while those resulting from *DGUOK* mutations include neonatal multisystem disorders and liver disorders in infancy or childhood [15, 16]. Some diseases are caused by large-scale mtDNA deletions, such as Pearson syndrome (PS) and Kearns-Sayre syndrome (KSS) [17].

Impaired mitobiogenesis leads to energy deficiency, which manifests as muscle weakness, muscle atrophy, and visual impairment, and is associated with spinal muscular atrophy (SMA), sarcopenia, and Leber hereditary optic neuropathy (LHON) [18-20]. The heart is the organ with the highest metabolic activity in the human body and contains the greatest concentration of mitochondria of any tissue [21]. The energy deficiency in heart failure is primarily attributed to dysregulation of PGC-1α [22]. In type 2 diabetes, insulin resistance is accompanied by downregulation of PGC-1α expression, ultimately leading to reduced oxidative capacity and lipid accumulation [23].

2.2. Diseases associated with defective mitophagy

Mitophagy selectively degrades damaged mitochondria and, together with mitobiogenesis, controls mitochondrial quality and mass [24]. Damaged mitochondria are recognized by autophagosomes, encapsulated, and subsequently degraded upon fusion with lysosomes [24]. Blocking mitophagy leads to the accumulation of dysfunctional mitochondria. This process occurs through two mechanisms: a ubiquitin-dependent manner and a ubiquitin-independent manner [25]. The former is primarily linked to the phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1)/Parkin signaling pathway. Following mitochondrial damage, PINK1 stabilizes on the OMM *via* the translocator of the outer membrane (TOM) complex, where it recruits and activates the E3 ubiquitin ligase Parkin [26]. Parkin then recruits mitophagy receptors, including sequestosome 1 (SQSTM1/p62), optineurin (OPTN), tax1-binding protein 1 (TAX1BP1), and nuclear dot protein 52 (NDP52). The binding of the mitophagy receptor to light chain 3 (LC3) enables the autophagosome to engulf mitochondria [25]. PINK1 can also directly induce mitophagy without Parkin by recruiting autophagy receptors [27]. Meanwhile, many receptors in the OMM bind directly to LC3 without ubiquitination to initiate mitophagy, including Nip3-like protein X (NIX), B-cell lymphoma-2 (Bcl-2)-interacting protein 3 (BNIP3), FUN14 domain-containing 1 (FUNDC1), and BCL2 like 13 (BCL2L13) [25].

FBXL4 restricts NIX and BNIP3 levels through direct interaction and protein destabilization, while dual-specificity phosphatase 1 (DUSP1) significantly decreases c-Jun N-terminal kinase (JNK) phosphorylation, thereby inactivating BNIP3 [28, 29]. The phosphorylation of FUNDC1 is primarily mediated by unc-51 like autophagy activating kinase 1 (ULK1) and casein kinase 2 (CK2), which promote phosphorylation of Ser17 and Ser13 respectively in FUNDC1, preventing its binding to LC3 [30]. Conversely, phosphoglycerate mutase family member 5 (PGAM5) dephosphorylates FUNDC1 at Ser13, an effect that CK2 can reverse [31]. MARCH5 binds to and ubiquitinates the Lys119 site of FUNDC1, inhibiting mitophagy [30]. Nuclear receptor subfamily 4 group A member 1 (NR4A1) inhibits FUNDC1-dependent mitophagy and also promotes dynamin-related protein 1/2 (Drp1)-mediated fission, highlighting the strong correlation within mitochondrial regulatory networks [32]. In addition, prohibitin 2 (PHB2) promotes PINK1/Parkin-mediated mitophagy *via* the presenilin-associated rhomboid-like (PARL)/PGAM5/PINK1 axis [33]. Phosphorylation of PHB2 at the Ser91/Ser176 sites can be further regulated by the piezo-type mechanosensitive ion channel component 1 (PIEZO1)/transmembrane Bax inhibitor motif containing 6 (TMBIM6) [34].

PINK1 and *PRKN* mutations consistently cause familial forms of Parkinson's disease (PD) [35]. *SQSTM1* mutations result in distinct diseases such as Paget's disease or neurodegeneration in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) [36]. Mutations in the ubiquitin-binding domain of *OPTN* impair Parkin-dependent mitophagy in ALS [37]. BNIP3/NIX-dependent mitophagy, which can be activated by HIF-1α, is associated with hypoxia-related diseases. For example, in tumors, high BNIP3/NIX expression driven by the hypoxic microenvironment can eliminate damaged mitochondria and promote metabolic reprogramming, which benefits cancer cell survival and enhances their resistance [38]. Dysfunctional mitophagy can also lead to neurodegenerative diseases by triggering neuroinflammation and oxidative stress [39].

2.3. Diseases associated with imbalanced mitochondrial dynamics

Mitochondrial dynamics refers to the process by which mitochondria undergo frequent cycles of fusion and fission to maintain their structure, shape, and size [2]. Mitochondrial fusion enables the redistribution of metabolites, proteins, and mtDNA, preventing the accumulation of damaged content within a single mitochondrion. This process is subdivided into OMM and IMM fusion. MFN undergoes a conformational change regulated by guanosine triphosphate (GTP) binding and hydrolysis, mediating OMM binding [2]. IMM-anchored long-OPA1 (L-OPA1) must undergo proteolytic cleavage to generate short-OPA1 (S-OPA1) isoforms, which work together to mediate IMM fusion [40].

MFN1/2 is primarily regulated by ubiquitination, mainly involving mitochondrial E3 ubiquitin ligase 1 (MUL1), mahogunin ring finger-1 (MGRN1), and Parkin. MGRN1 regulates the ubiquitination of MFN1, while MUL1 and Parkin act on MFN2, which is associated with neurodegenerative diseases and cardiomyocyte hypertrophy [41]. Conversely, to stabilize MFN, ubiquitin-specific protease 30 (USP30) and USP35 remove ubiquitin chains from MFN [42]. OPA1 is primarily regulated by proteolytic cleavage, involving yeast mitochondrial escape 1-like ATPase (YME1L) and overlapping activity with m-AAA protease-1 (OMA1). Mitochondrial depolarization coupled with ATP depletion stabilizes OMA1, whereas depolarization alone triggers YME1L-mediated degradation of OMA1 [43].

Currently, fusion abnormalities are mainly described as mitochondrial fusion deficiency. *MFN2* deletion mutations cause Charcot-Marie-Tooth disease subtype 2A (CMT2A), a genetic disorder characterized by progressive muscle weakness and distal limb atrophy [2]. *OPA1* mutations cause autosomal dominant optic atrophy (ADOA), which manifests as optic neuropathy [44]. OPA1 is essential for maintaining normal neuronal function and morphology; therefore, it is closely associated with neurodegenerative diseases [44]. In addition, MFN2 is highly expressed in the heart, and its absence may result in cardiac dysfunction [45].

Mitochondrial fission is subdivided into midzone and peripheral fission [46]. Fis1 regulates lysosomal function to promote peripheral fission, ensuring that dysfunctional mitochondria are degraded *via* mitophagy. Midzone fission, linked to the ER, generates new mitochondria to support cell proliferation or increased energy demands. This process is driven by Drp1 binding directly to actin filaments, which coactivates Drp1 with MFF [46]. Both types of fission involve Drp1. MiD49 and MiD51 participate in both types of fission but are not required [46].

Phosphorylation of Ser616 activates Drp1, promoting mitochondrial fission, while phosphorylation of Ser637 inhibits Drp1 activity. Proteins that phosphorylate Ser616 include cyclin-dependent kinase 1 (CDK1), JNK1, and extracellular signal-regulated kinases 1/2 (ERK1/2) [47-49]. Syntaxin 17 recruits CDK1 to mitochondria-associated ER membranes, promoting Drp1 activity and preventing heart failure [48]. Downregulation of SIRT2 increases acetylation of mitogen-activated protein kinase (MAPK) kinase-1 (MEK1) at Lys175, activating the ERK/Drp1 axis, and it also hyperacetylates Akt1 at Lys20, which directly activates Drp1 [49]. A-kinase anchoring protein 121 (AKAP121) provides neuroprotection by recruiting protein kinase A (PKA), which phosphorylates Ser637 of Drp1 to stabilize mitochondrial fusion [50]. MFF is primarily regulated through direct phosphorylation by AMPK, which enhances its capacity to recruit Drp1 [51].

Under pathological conditions, excessive peripheral fission leads to mitochondrial fragmentation, causing metabolic, cardiovascular, and neurodegenerative diseases [7]. In contrast, excessive midzone fission can result in increased cell proliferation associated with tumor progression [46]. *DNM1L* encodes Drp1; its de novo heterozygous pathogenic variants are associated with neonatal/infantile encephalopathy with hypotonia, developmental delay, and refractory epilepsy [52]. Causative genes also associated with encephalopathy, optic atrophy, and peripheral neuropathy include *MFF*, highlighting the crucial role of regulating mitochondrial fission in brain development [53].

2.4. Diseases associated with OXPHOS dysfunction

OXPHOS, the primary source of ATP in eukaryotic cells, couples electron transport with the generation of a proton gradient across the IMM to drive ATP synthesis [54]. Complex I-V (CI-CV) are involved in the mitochondrial electron transport chain (ETC). Under physiological conditions, 0.2%−2% of electrons escape the ETC and interact with oxygen to generate reactive oxygen species (ROS). CI and CIII, especially CI, are considered the major sites of ROS production in mitochondria [54].

Some OXPHOS regulators have been identified as potential targets for improving mitochondrial function. Zinc-finger and homeoboxes 2 (ZHX2) transcriptionally inhibits the expression of several ETC genes, reducing the stability of PGC-1α and inhibiting OXPHOS [55]. Conversely, nuclear myosin 1 (NM1) directly promotes OXPHOS by regulating PGC-1α [56]. SIRT3 activates CI and CII, while PKA phosphorylates CI subunits to reduce ROS production [57, 58].

Dysfunctional OXPHOS is often caused by mutations in mtDNA or damage to ETC components. Leigh syndrome, a mitochondrial encephalopathy in children, is associated with over 75 gene mutations involved in CI-CIV and assembly factors, and presents with progressive neurological decline and poor prognosis [59]. Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is primarily caused by mutations in the mitochondrial $tRNA^{Leu(UUR)}$ gene [60]. Myoclonus epilepsy with ragged-red fibers (MERRF) is associated with variations in the mitochondrial $tRNA^{Lys}$ gene [60]. *BCS1L* is essential for CIII synthesis; its mutations consistently cause heterogeneous multisystem disorders [61].

The body primarily experiences muscle weakness, ophthalmoplegia, and myocardial injury due to energy deficiency following abnormal OXPHOS [62]. Meanwhile, ROS accumulation leads to oxidative stress, resulting in neurodegenerative diseases and cardiomyopathy [63, 64]. Abnormal OXPHOS often increases the $NADH/NAD^+$ ratio, stimulates glycolysis, and ultimately results in severe lactic acidosis [65].

2.5. Diseases associated with mitochondrial Ca^{2+} dyshomeostasis and dysregulated mitochondria-mediated apoptosis

Apoptosis is a spontaneous and orderly process of cell death that maintains internal homeostasis under physiological and pathological conditions. The regulation of apoptosis is divided into the endogenous mitochondrial pathway and the exogenous death receptor pathway [66]. Mitochondria-mediated apoptosis can be further classified into caspase-dependent and caspase-independent pathways, mediated by signaling molecules such as oxidative stress, Cyt-c, and Ca^{2+} [67, 68].

The concentration of Ca^{2+} is critical for maintaining mitochondrial membrane permeability. When Ca^{2+} concentration in the matrix increases, calpain and calcineurin are activated. Calpain cleaves Bid, and calcineurin dephosphorylates Bad [69, 70]. Their activation leads to the sequestration of anti-apoptotic family proteins and the translocation of pro-apoptotic family proteins [66]. Subsequently, Cyt-c is released into the cytoplasm, where it binds to apoptotic protease-activating factor 1 (Apaf1) to form apoptosomes. Caspase-9 is recruited and activated, promoting the activation of caspase-3 and caspase-7, leading to apoptosis [66]. Inhibitors of apoptosis (IAPs) can inhibit this process. Second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI (Smac/DIABLO) and HtrA2/Omi can bind to IAPs

and neutralize their inhibitory effect on caspases [6, 66]. Caspase-independent apoptosis is mainly associated with apoptosis-inducing factor (AIF) and endonuclease G (Endo G) released through MOMP [68].

High ER stress disrupts Ca^{2+} homeostasis and intensifies mitochondria-mediated apoptosis. During ER stress, cells initiate the unfolded protein response (UPR) to clear misfolded proteins and restore ER homeostasis. The UPR consists of three core signaling pathways: inositol-requiring enzyme 1 (IRE1)/X-box-binding protein 1 (XBP1), protein kinase RNA-like ER kinase (PERK)/eukaryotic initiation factor 2 alpha (eIF2α)/activating transcription factor 4 (ATF4), and ATF6 [71]. Similarly, damaged mitochondria initiate a specialized UPR, termed UPRmt. The UPR and UPRmt jointly integrate stress signals to determine cell fate [72]. The dynamic balance between mitophagy and UPRmt is crucial for mitochondrial and cellular homeostasis. FUNDC1-mediated mitophagy remains active even when UPRmt is inhibited; however, this balance is disrupted in ischemic myocardium [73]. The absence of FUNDC1 leads to the downregulation of key UPRmt factors and cardiac impairment, which can be reversed by the overexpression of ATF5 [74].

Under pathological conditions, mitochondrial Ca^{2+} overload increases ROS production. The combined increase in Ca^{2+} and ROS triggers mPTP opening, leading to apoptosis [67]. Developmental delay, learning disorders, and muscle weakness result from *MICU1* mutations, as *MICU1* encodes the regulatory subunit of the mitochondrial calcium uniporter [75]. In addition, as the key signal for cardiac excitation-contraction coupling, weakened cytosolic Ca^{2+} transients directly impair myocardial contractility [76]. In neurodegenerative diseases, abnormal contact between the ER and mitochondria decreases mitochondrial Ca^{2+} buffering capacity, exacerbating excitotoxicity and oxidative stress [77].

2.6. The complex regulatory network of mitochondria

These processes do not occur in isolation in actual diseases. Cardiac endothelial dysfunction is a significant cause of CVDs and is closely associated with mitochondrial abnormalities in endothelial cells [78, 79]. Cardiac endothelial dysfunction illustrates how multiple mitochondrial defects drive disease progression.

Mitochondrial dysfunction is typically triggered and exacerbated by common cardiovascular risk factors such as unhealthy diets, smoking, lack of exercise, poor sleep, and excessive alcohol consumption [80]. Upon stimulation, endothelial cells in the coronary arteries are the first to be affected, where mitochondrial dynamics is disrupted, resulting in excessive Drp1 activation [78]. The recruitment of Drp1 is a critical step in initiating mitophagy [81]. Accumulated damaged mitochondria trigger excessive mitochondrial ROS production, which suppresses mitobiogenesis and directly induces mitochondria-mediated apoptosis, ultimately leading to endothelial dysfunction [81]. Abnormal endothelial signals and insufficient perfusion cause myocardial ischemia/reperfusion (I/R) injury. In cardiomyocytes, hypoxia/ischemia inhibits OXPHOS, reduces ATP synthesis, causes Ca^{2+} overload and mPTP opening, and triggers apoptosis [82].

Failure of spatial positioning further amplifies this vicious cycle. In cardiomyocytes, mitochondria rely on the microtubule network for precise movements that enable on-demand energy production and distribution. Furthermore, the direct physical binding of tubulin to VDAC dynamically regulates mitochondrial metabolic flux and energy flow [83]. The imbalance between microtubules and mitochondria disrupts cellular energy distribution, drives cell death, and worsens heart failure. Multitarget interventions are key to breaking this vicious cycle, which explains the therapeutic potential of natural products.

3. Natural products targeting mitochondria

3.1. Natural products targeting impaired mitobiogenesis

Natural products that activate mitobiogenesis are an important intervention strategy for heart failure, metabolic disorders, and fatigue [21, 22]. As the core regulator of mitobiogenesis, PGC-1α is primarily modulated by factors such as AMPK, SIRT1, and PPARγ (Fig. 1, Supplementary Table S1).

Natural products present a promising therapeutic strategy for metabolic disorders. Salidroside (SAL) has shown positive effects in treating diabetes-related diseases. It improves cardiac function and glucose levels by phosphorylating AMPK, which increases SIRT3 and restores PGC-1α/TFAM expression, thereby enhancing mitobiogenesis and antioxidant defense [84]. In diabetic nephropathy mice, SAL also significantly reverses the decrease in SIRT1 and PGC-1α [85]. Additionally, SAL delays aging in human fibroblasts by upregulating SIRT1/PGC-1α [86]. These findings suggest that the precise mechanism may differ across various tissues or diseases. Berberine (BBR), an AMPK agonist, significantly increases glucose uptake in insulin-resistant cells, improving insulin resistance [87]. Numerous clinical trials on BBR for metabolic diseases have been conducted, but few have yielded results due

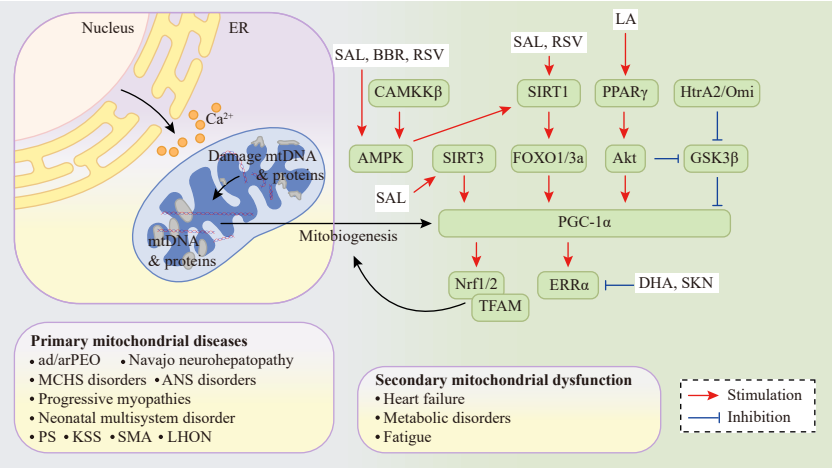


Fig. 1 Natural products targeting mitobiogenesis. White boxes indicate natural products and their potential mechanisms for regulating mitobiogenesis. Green boxes indicate mitobiogenesis-related proteins. PGC-1α is the key factor in mitobiogenesis, and several mitobiogenesis-related signaling pathways are associated with PGC-1α. Salidroside (SAL), berberine (BBR), and resveratrol (RSV) act as AMPK agonists. Among these, SAL can also upregulate SIRT1 and SIRT3. RSV upregulates SIRT1, and lauric acid (LA) is a PPARγ agonist. Dihydroartemisinin (DHA) and shikonin (SKN) inhibit mitobiogenesis by blocking ERRα.

to its low bioavailability [88].

A reduction in mitochondrial production is positively correlated with decreased muscle or physical endurance. Ursolic acid (UsA) increases mitobiogenesis by upregulating AMPK/PGC-1α in skeletal muscle, thereby enhancing exercise endurance [89]. A phase II clinical trial has been completed to evaluate whether UsA can reduce muscle loss [90]. Resveratrol (RSV) effectively promotes muscle regeneration by activating PGC-1α and enhancing myogenic differentiation [91]. In addition, RSV undergoes rapid and extensive metabolism into inactive glucuronides, resulting in nearly negligible bioavailability [92].

The AMPK signaling pathway is an ideal target for CVDs, and the protective effects of natural AMPK agonists such as ginsenoside Rh4 (GRh4) and *β*-lapachone (*β*-LAP) have confirmed this potential [93, 94]. The PPARγ/Akt/PGC-1α pathway is another core signaling axis, which often interacts with the AMPK/SIRT1/PGC-1α pathway. Δ^9-tetrahydrocannabinolic acid (Δ^9-THCA) stimulates PPARγ-dependent mitobiogenesis to mediate neuroprotection [95]. Rosiglitazone, a clinical PPARγ agonist for diabetes, is effective but has side effects. Lauric acid (LA) at 20 μmol·L^{-1} is comparable to 10 μmol·L^{-1} of rosiglitazone in restoring mitochondrial content in insulin-resistant macrophages, suggesting a new approach to developing safer regulators of the PPARγ pathway [96].

PGC-1α is also regulated by ERRα. Inhibiting mitobiogenesis can suppress tumor growth by depleting mitochondria in cancer cells. Dihydroartemisinin (DHA) inhibits glioma growth by blocking ERRα-mediated mitobiogenesis [97]. Shikonin (SKN) inhibits mitobiogenesis by impeding PGC-1α expression, nuclear localization, and its interaction with ERRα, thereby blocking cancer metastasis [98]. In summary, natural products can exert bidirectional influences on cell fate, enhancing the functions of normal cells or inhibiting the proliferative potential of pathological cells.

3.2. Natural products targeting mitophagy

Impaired mitophagy often triggers hypoxia-related diseases, such as tumors, neurodegenerative diseases, and inflammation [38, 39]. Natural products can regulate mitophagy in both directions by interfering with key pathways, such as PINK1/Parkin (Fig. 2, Supplementary Table S2). These products induce mitophagy to remove damaged organelles and inhibit excessive mitophagy to prevent unnecessary loss of healthy mitochondria.

Accumulation of damaged mitochondria in neurons leads to energy deficiency, resulting in neurodegenerative diseases. BBR acts as an epigenetic regulator to restore PINK1/Parkin-mediated mitophagy by inhibiting methylation of the PINK1 promoter, thereby protecting nerves [99]. Tetrahydroberberrubine (THBru) delays cardiomyocyte senescence by overexpressing PHB2, a key mediator of PINK1-dependent mitophagy in heart diseases [100]. One proposed mechanism links cardiac mitochondrial dysfunction to impaired binding between PHB2 and DUSP1. Astragaloside IV (As IV) can reverse heart damage by restoring this interaction and can also reverse excessive mitochondrial fragmentation during mitophagy after inflammation [101, 102].

Natural products can also modulate ubiquitin-independent mitophagy, which involves NIX, BNIP3, or FUNDC1, and is usually associated with hypoxia-related diseases. Tanshinone I (Tan I) significantly increases the expression of BNIP3 and NIX, inhibiting the metastasis of cervical cancer cells [103]. Artesunate (ART) inhibits FUNDC1 phosphorylation, which further activates mitophagy in sorafenib-resistant cells, enhancing the inhibitory effect of sorafenib on tumors [104]. Gypenoside A (GypA) activates FUNDC1 phosphorylation at Tyr18, normalizes mitophagy, and restores cardiomyocyte viability [105]. Modulating mitophagy offers a potential therapeutic avenue for addressing metabolic diseases. Fucoxanthin (FX) enhances BNIP3-mediated mitophagy and has been evaluated in a phase II clinical trial for metabolic syndrome [106, 107]. This may be a potential treatment strategy for reducing abdominal fat accumulation.

Mitophagy plays a dual role in tumor development, removing damaged mitochondria to reduce oxidative stress in normal cells and restricting the release of oxidative substances from damaged mitochondria, which increases drug resistance in tumor cells [108]. Excessive mitophagy may also exacerbate mitochondrial damage, leading to neuronal apoptosis [109]. Therefore, inhibiting mitophagy may be beneficial in specific contexts. Thymoquinone (TQ), which decreases PINK1 and thus inhibits mitophagy, has a protective effect against cigarette smoke extract-induced abnormalities in bronchial epithelial cells [110]. Aloe emodin (AE) alleviates radiation-induced heart damage by inactivating NDP52-induced mitophagy [111]. Isovitexin (IVT) significantly inhibits BNIP3/NIX-induced mitophagy by restoring SIRT3 expression [112]. Liensinine (LIE) inhibits late-stage mitophagy by blocking the fusion of autophagosomes with lysosomes [113].

Celastrol (CEL) can block the recruitment of Parkin to mitochondria and interfere with the binding of PINK1 and TOM20,

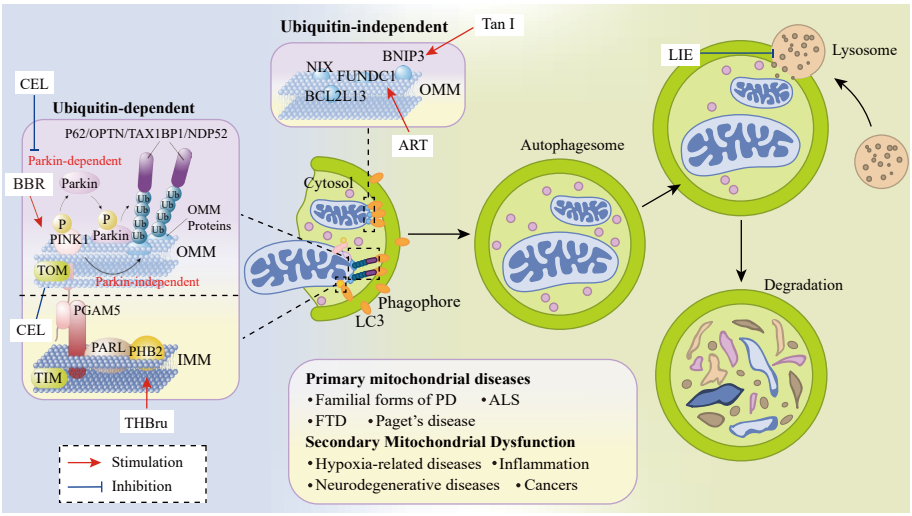


Fig. 2 Natural products targeting mitophagy. White boxes indicate natural products and their potential mechanisms for regulating mitophagy. Damaged mitochondria are recognized and enclosed by the autophagosome, which then fuses with the lysosome to degrade the contents. BBR restores PINK1/Parkin-mediated mitophagy by inhibiting methylation of the PINK1 promoter, while celastrol (CEL) inhibits PINK1/Parkin-mediated mitophagy. Tetrahydroberberrubine (THBru) promotes mitophagy by overexpressing PHB2. Tanshinone I (Tan I) significantly increases BNIP3 and NIX. Artesunate (ART) promotes FUNDC1-mediated mitophagy. Liensinine (LIE) inhibits late-stage mitophagy by preventing the fusion of autophagosomes and lysosomes.

preventing mitophagy [114]. Meanwhile, CEL can promote the transfer of Nur77 to the mitochondria, stimulating mitophagy and reducing inflammation [115]. Melatonin (MLT) ameliorates cognitive impairment by inhibiting excessive mitophagy and also induces mitophagy in liver fibrosis [116]. This highly condition-dependent characteristic of natural products presents a significant challenge in studying their impact on mitochondria.

3.3. Natural products targeting mitochondrial dynamics

Imbalances in mitochondrial dynamics often present as defects in mitochondrial fusion and excessive fragmentation, which are associated with CVDs, neurodegenerative diseases, and tumors (Fig. 3) [7]. Some natural products can promote mitochondrial fusion and inhibit fission (Supplementary Table S3). Promoting mitochondrial fusion mainly involves upregulating MFN1/2 and OPA1, which helps remodel mitochondria in the heart and nervous system. Breviscapine (BRE) promotes MFN1-mediated fusion by attenuating FOXO3a phosphorylation, thereby inhibiting cardiac hypertrophy [117]. Interestingly, BRE also alleviates liver I/R injury by downregulating MFN2 [118]. Hyperoside (HPS) suppresses OPA1 proteolysis, preventing the formation of excessive S-OPA1 and thus inhibiting mitochondrial fission [119]. Paeonol (PAE) targets PKCε, leading to STAT3 phosphorylation. Activated STAT3 binds to the MFN2 promoter, promoting MFN2-mediated fusion and restoring cardiac function [120]. Matrine (MAT) acts as a SIRT3 agonist and regulates OPA1 acetylation [121].

During ischemic injury, inhibiting excessive pathological mitochondrial fission can protect the cardiovascular and nervous systems. Diallyl trisulfide (DATS) and mangiferin (MANG) activate AMPK, downregulating Drp1 expression to maintain vascular homeostasis [122, 123]. Cordycepin (CY) also reverses Drp1-mediated fission by increasing AMPK phosphorylation, providing neuroprotection [124]. Increasing Drp1 levels is also a therapeutic strategy. For example, caffeine (CAF) induces mitochondrial fission, increases the number of mitochondria required for cell migration, and significantly promotes angiogenesis and perfusion in ischemic hind limbs [125]. Inducing mitochondrial fission in tumor cells can promote apoptosis and inhibit tumor growth. Baicalein (BAI) and kaempferol (KAE) induce Drp1-mediated fission by activating AMPK, exhibiting anticancer effects [126, 127]. Natural products can also increase the sensitivity of cells to traditional anti-tumor treatments. Salvianolic acid B (SalB) significantly promotes mitochondrial fission, exacerbating radiation-induced apoptosis and mitochondrial dysfunction, while piceatannol (PTL) enhances the sensitivity of ovarian cancer cells to cisplatin [128, 129]. More natural products inhibit mitochondrial fission while promoting mitochondrial fusion, such as ginsenoside Rg1 (GRg1) and BAI [130, 131]. The application of natural products should be tailored to specific diseases, as mitochondrial dynamics requires precise regulation.

3.4. Natural products targeting OXPHOS

3.4.1. ETC inhibitors

Some tumor cells are more sensitive to OXPHOS inhibitors, making ETC inhibition a potential therapeutic strategy for cancer [132]. ETC inhibitors mainly target CI-CIV (Fig. 4, Supplementary Table S4). Rotenone (ROT) inhibits CI and blocks electron transfer from NADH to ubiquinone (CoQ), serving as a potential anticancer agent [132]. Recent research shows that BBR inhibits CI and OXPHOS to manage dyslipidemias. It directly binds to and activates SIRT3, reducing NDUFS1 acetylation and thereby mediating CI dissociation [133]. Gracillin (GRA) disrupts CII function by abrogating succinate dehydrogenase activity, while miltirone (MTR) triggers ROS generation by dose-dependently inhibiting CIII activity [134, 135].

3.4.2. Uncoupling protein (UCP) modulators

Uncoupled respiration, mainly mediated by UCPs, occurs when proton flow is uncoupled from ATP synthesis, allowing mitochondria to dissipate the proton gradient as heat [54]. UCP1 primarily plays an adaptive thermogenic role in brown adipose tissue, while UCP2 and UCP3 prevent mitochondrial oxidative damage by reducing ROS production [54]. UCP1 dysregulation is associated with metabolic disorders such as obesity. Curcumin (CUR) significantly increases UCP1 expression in brown adipose tissue and simultaneously reduces fat accumulation, liver weight, and metabolic abnormalities [136]. Some natural products, such as theobromine (TB), act as PPARγ agonists, thereby increasing UCP1 [137]. UCP2 suppresses ROS production by facilitating increased electron flux, which protects against apoptosis [54]. Alisol A (AA) upregulates UCP2 to inhibit oxidative stress, protecting

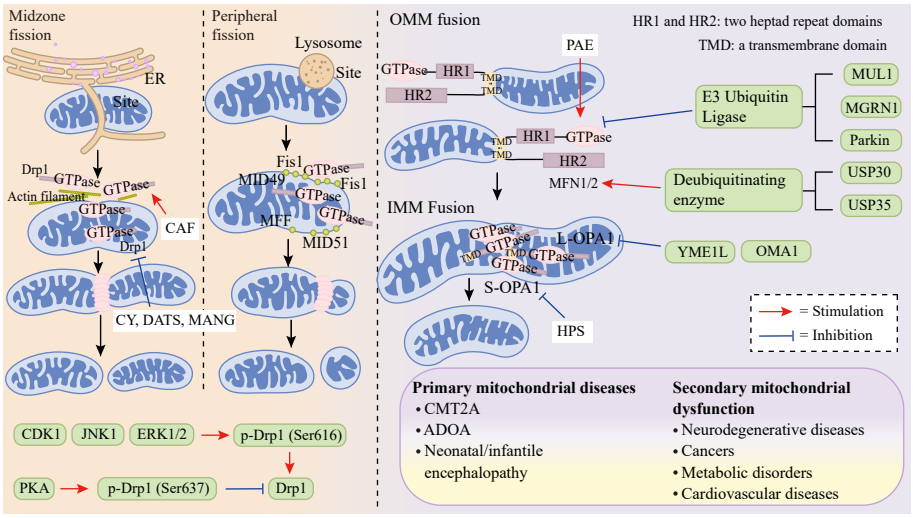


Fig. 3 Natural products targeting mitochondrial dynamics. White boxes indicate natural products and their potential mechanisms for regulating mitochondrial dynamics. Green boxes indicate mitochondrial dynamics-related proteins. Mitochondrial dynamics includes fusion and fission. Fusion involves OMM and IMM fusion, while fission is subdivided into midzone and peripheral fission. MFN can be degraded by E3 ubiquitin ligases. Conversely, USP30 and USP35 stabilize MFN as deubiquitinating enzymes. Paeonol (PAE) can induce MFN2-mediated mitochondrial fusion. YME1L and OMA1 jointly regulate OPA1 proteolysis. Hyperoside (HPS) inhibits mitochondrial fission induced by OPA1 protein hydrolysis. Drp1 activity is associated with phosphorylation at Ser616 and Ser637. Cordycepin (CY), diallyl trisulfide (DATS), and mangiferin (MANG) suppress Drp1, while caffeine (CAF) induces mitochondrial fission *via* Drp1 activation.

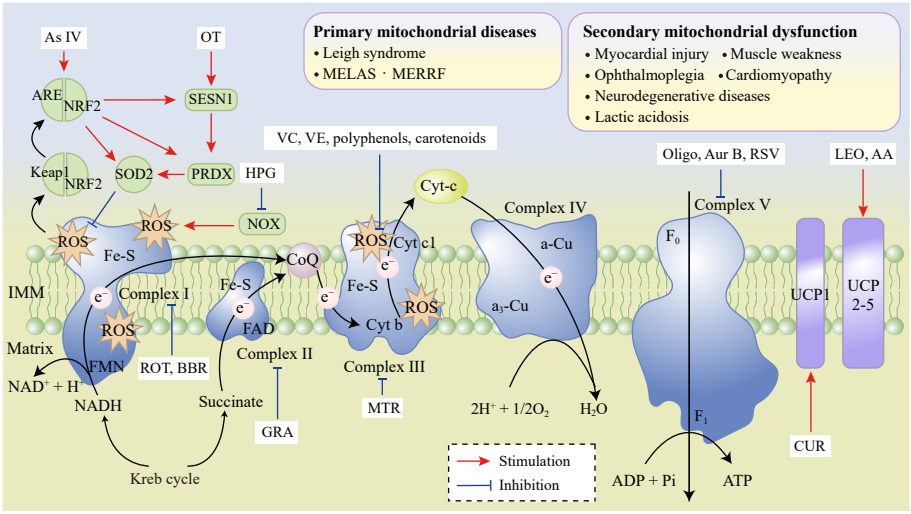


Fig. 4 Natural products targeting oxidative phosphorylation (OXPHOS). White boxes indicate natural products and their potential mechanisms for regulating OXPHOS. Green boxes indicate OXPHOS-related proteins. The electron transport chain (ETC) generates ATP through OXPHOS. Rotenone (ROT) and BBR inhibit the activity of complex I. Gracillin (GRA) inhibits complex II, while miltirone (MTR) inhibits complex III. CUR acts as a UCP1 agonist. Leonurine (LEO) and alisol A (AA) upregulate UCP4 and UCP2, respectively, exerting antioxidant effects. Inhibitors of complex V include oligomycin (Oligo), aurovertin B (Aur B), and some polyphenols like RSV. Antioxidants mainly include vitamins (Vitamin C and E), polyphenols, and carotenoids. Astragaloside IV (As IV) promotes the dissociation of NRF2 from the Keap1-NRF2 complex to exert antioxidant effects. Harpagoside (HPG) reduces NOX2 and NOX4 levels, while orientin (OT) increases SESN1 levels.

neurons [138]. UCP4 and UCP5 also alleviate oxidative stress and are mainly associated with neuroprotection due to their localization on the IMM of neurons [139]. Leonurine (LEO) significantly alleviates neurological dysfunction following ischemic stroke, accompanied by increased UCP4 activity [140].

3.4.3. ATP synthase inhibitors

Action on CV regulates ATP synthesis and OXPHOS, thereby influencing energy metabolism. Similar to ETC inhibitors, several microorganism-derived natural products exhibit anticancer effects, including citreoviridin (CTV), apoptolidin (Apo), ossamycin (Ossa), oligomycin (Oligo), aurovertin B (Aur B), mandelalide A (Man A), and cruentaren A (Cru A) [141-145]. Polyphenols, such as RSV and PTL, also inhibit ATP synthase by targeting the F_1 catalytic headpiece [146]. Genistein (GEN) and biochanin A (BCA) noncompetitively inhibit both ATP hydrolysis and synthesis activities of ATP synthase, most likely by targeting F_0 [147].

3.4.4. Antioxidants

Some natural products act at various points in the OXPHOS process rather than binding to a single target, such as antioxidants that reduce oxidative stress. These products, commonly used as dietary supplements, are mainly vitamins (vitamin C and E), polyphenols, and carotenoids [148]. Vitamin E, a lipid-soluble vitamin, has low bioavailability and requires dietary fat for absorption, so it is best taken with meals [149]. Most polyphenols also have low bioavailability due to rapid metabolism and clearance, while carotenoid absorption is affected and limited by multiple physiological factors [150, 151].

Nuclear factor erythroid 2-related factor 2 (NRF2), the main regulatory factor, activates glutathione biosynthesis by binding to antioxidant response elements (ARE) and regulates the mitochondrial antioxidant enzyme superoxide dismutase 2 (SOD2). NRF2 activation is negatively regulated by Kelch-like ECH-associated protein 1 (Keap1) ubiquitination [152, 153]. As IV promotes NRF2 dissociation from the Keap1-NRF2 interaction by competitively binding to amino acid sites in Keap1 [153]. The NADPH oxidase (NOX) family is the primary source of ROS. Harpagoside (HPG) reduces ROS generation by inhibiting NOX2 and NOX4 [154]. A decrease in peroxiredoxin 6 (PRDX6) expression activates the NF-κB signaling pathway, which is associated with excessive ROS production. CUR can restore PRDX6 levels and alleviate oxidative stress damage [155]. Sestrins (SESNs) can counteract oxidative stress, leading to AMPK activation and reduced mTOR expression. Orientin (OT) can increase SESN1 to regulate the AMPK/mTOR signaling pathway [156].

3.5. Natural products improving Ca^{2+} homeostasis and mitochondria-mediated apoptosis

3.5.1. Natural products stimulating ROS production, Ca^{2+} elevation, and mitochondrial membrane potential ($\Delta\Psi m$) disruption

Increased intracellular ROS levels cause ΔΨm collapse, ultimately initiating apoptosis [67]. Promoting apoptosis is beneficial for cancer treatment. Ainsliadimer A (AIN) directly targets Cys173 of PRDX1 and Cys172 of PRDX2, resulting in increased ROS production and mitochondria-mediated apoptosis [157]. Ponicidin (PON) targets Keap1 and promotes the formation of the Keap1-PGAM5 complex, leading to ROS production [158]. Silibinin (SIL) triggers mitochondrial ROS production through NOX4 expression and ultimately induces apoptosis [159]. Certain natural products exhibit dual dose-dependent effects. In the human lymphocyte system, at high doses, some flavonoids act as antioxidants, whereas at low doses they promote ROS generation and apoptosis [160]. However, their exact concentration thresholds need further characterization.

Using natural products to intervene in ER stress is also a potential therapeutic strategy. Chrysin (CHR) induces mitochondria-mediated apoptosis and ER stress by activating PERK/eIF2α, thereby regulating the proliferation of prostate cancer cells [161]. Sarcoplasmic/ER calcium ATPase (SERCA) is the primary regulator of intracellular Ca^{2+}. Its inhibition by saikosaponin D (SSD) disrupts Ca^{2+} homeostasis, leading to ER stress and subsequent mitochondria-mediated apoptosis [162].

3.5.2. Natural products stimulating mitochondria-mediated apoptosis by targeting proteins involved in this pathway

Some natural products activate pro-apoptotic proteins or inhibit anti-apoptotic proteins, producing tumor-inhibitory effects. Activation of Bcl-2-homology domain 3 (BH3)-only proteins (Bad/Bid) can also stimulate pro-apoptotic proteins. Gossypol (GSP) acts as a BH3-mimetic, binding to the BH3 pocket of anti-apoptotic proteins to induce apoptosis [163]. GSP and its derivatives have been widely studied in clinical trials and are classic examples of agents that directly target Bcl-2 proteins. Quercetin

(QR) induces the proteasomal degradation of anti-apoptotic protein Mcl-1, restoring tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) sensitivity in resistant lymphoma cells [164]. Embelin (EBL) decreases the interaction between X-linked IAP (XIAP) and caspase-3, thereby enhancing caspase activity [165]. Adenine nucleotide translocase (ANT) and cyclophilin D (CypD) are core components of the mPTP [5]. Bufarenogin (BFG) induces mitochondria-mediated apoptosis through the cooperation of Bax and ANT [166]. Atractyloside (ATR) is an ANT ligand that induces permeability transition and mPTP opening [167]. CHR induces apoptosis by reducing hexokinase 2 (HK2), which binds to VDAC to prevent apoptosis of cancer cells on the OMM [168]. Naphthazarin (DHNQ) prevents the accumulation of the reduced form of AIF, thereby promoting caspase-independent apoptosis [169].

3.5.3. mPTP inhibitors and Ca^{2+} homeostasis regulators

Bongkrekic acid (BKA) targets ANT to maintain its "m" conformation, thereby inhibiting mPTP opening and reducing apoptosis [170]. Cyclosporin A (CsA) selectively inhibits CypD by blocking its binding to ANT [171]. Pubescenoside D (PBD) inhibits mPTP opening by preventing HK2 dissociation from the OMM, reducing cardiomyocyte apoptosis [172]. SERCA activators primarily protect the myocardium and skeletal muscle by inhibiting apoptosis. Salvianolic acid A (SalA) and luteolin (LUT) both increase SERCA activity and expression, thereby improving cardiac dysfunction [173,174]. Furthermore, there is a close correlation between UPR and mitochondria-mediated apoptosis. Tan IIA alleviates Ca^{2+} overload through the UPR pathway mediated by methyltransferase-like 3 (METTL3), which is upregulated after ER stress and mediates UPRmt [72]. Ginsenoside Rb1 (GRb1) improves cerebral ischemic injury by directly binding to the kinase domain of IRE1, reducing ischemia-induced apoptosis [175].

3.5.4. Natural products inhibiting mitochondria-mediated apoptosis by targeting proteins involved in this pathway

An increased Bcl-2/Bax ratio and inhibition of caspases have anti-apoptotic effects that protect organs. Parthenolide (PNL) prevents mitochondria-mediated apoptosis by increasing the expression of bromodomain-containing protein 4 (BRD4) and Bcl-X_L, thereby improving sepsis-induced coagulopathy [176]. Nigranoic acid (NGA) inhibits caspase-independent apoptosis in neurons by preventing the nuclear translocation of AIF [177].

In conclusion, natural products targeting mitochondria-mediated apoptosis have enormous therapeutic potential (Fig. 5, Supplementary Table S5). However, their application faces several challenges. These products can cause systemic toxicity if diseased tissues cannot be precisely distinguished from normal tissues. Therefore, accurately defining the therapeutic concentration threshold and designing appropriate administration schemes are essential for successful clinical translation.

4. Natural products in multitarget pathway regulation

It is important to note that the effects of natural products work together within a highly interconnected cellular signaling network. CUR provides neuroprotection by coordinately regulating multiple mitochondrial biological processes. CUR can restore the decline of PGC-1α under pathological conditions, maintain mitobiogenesis, and alleviate neural damage [178]. Following modification of CUR formulation with biomimetic nanoparticles, CUR can effectively target damaged neuronal mitochondria in an inflammatory environment and modulate the SIRT1/PGC-1α pathway to alleviate neuronal toxicity [178]. CUR activates mitophagy by regulating the PINK1/Parkin signaling pathway, and restores mitochondrial dynamics [179]. CUR reduces the release of Cyt-c, alters Bcl-2 family expression, and alleviates neuronal apoptosis, accompanied by reduced ROS levels [180]. These pathways form an interlocking network, enabling CUR to demonstrate a synergistic and systemic protective effect in neurodegenerative diseases.

However, these mechanisms function only when CUR concentration is low. High doses of CUR usually trigger acute responses, including autophagy and cell death [181]. This suggests that tissue targeting of natural products deserves further study. Similarly, RSV also exhibits this dual effect. In ECV304 cells, RSV induces cell death at high concentrations (> 20 μmol·L^{-1}), but not at low concentrations (0.1–20 μmol·L^{-1}) [182].

5. Clinical translation and pharmacokinetics of natural products

Despite their success in drug discovery, few natural products have reached the market due to challenges in clinical translation.

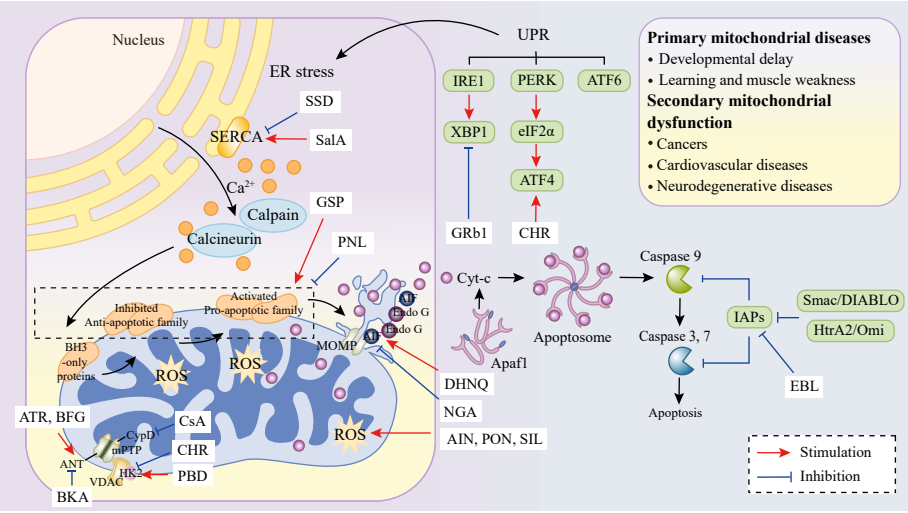


Fig. 5 Natural products targeting mitochondria-mediated apoptosis. White boxes indicate natural products and their potential mechanisms for regulating mitochondria-mediated apoptosis. Green boxes indicate apoptosis-related proteins. Mitochondria-mediated apoptosis is mainly triggered by the regulation of ROS and Ca^{2+} signaling. Ainsliadimer A (AIN), ponicidin (PON), and silibinin (SIL) induce apoptosis by promoting mitochondrial ROS production. Gossypol (GSP) directly inhibits anti-apoptotic proteins, thereby inducing apoptosis. Additionally, naphthazarin (DHNQ) induces AIF-dependent apoptosis. Saikosaponin D (SSD) inhibits SERCA and disrupts Ca^{2+} homeostasis, leading to mitochondria-mediated apoptosis. Chrysin (CHR) activates PERK/eIF2α and induces mitochondria-mediated apoptosis. Embelin (EBL) enhances apoptosis by reducing the interaction between XIAP and caspase-3. Atractyloside (ATR), bufarenogin (BFG), and CHR trigger the opening of the mPTP, while bongkrekic acid (BKA), cyclosporin A (CsA), and pubescenoside D (PBD) have the opposite effect. Salvianolic acid A (SalA) enhances SERCA activity and expression, improving Ca^{2+} homeostasis. Ginsenoside Rb1 (GRb1) inhibits IRE1 phosphorylation and reduces apoptosis. Parthenolide (PNL) and nigranoic acid (NGA) inhibit caspase-dependent and caspase-independent mitochondria-mediated apoptosis, respectively.

To achieve commercialization, they must demonstrate high bioavailability, well-defined safety profiles, and precise efficacy.

For example, CUR exhibits excellent anti-inflammatory and antioxidant properties but has extremely low oral bioavailability. Various approaches have been attempted, including structural modification, improved formulation, and combination with other products. Novel CUR derivatives have shown higher water solubility and greater bioavailability [183]. CUR encapsulated in phospholipids has demonstrated significantly improved systemic absorption and delivery [184]. Co-administration of CUR with piperine significantly increased CUR concentration and enhanced its bioavailability by 2000% [185]. Due to enhanced bioavailability, CUR is now in clinical trials, with a phase II trial currently evaluating new formulations or nanoparticles [186].

Another example of dosage form improving bioavailability is silymarin (SMR, Legalon). Formulated from Eurosil 85, it exhibits high oral bioavailability and defined pharmacokinetic and pharmacodynamic properties [187]. Legalon enhances the bioavailability of silymarin *via* phospholipid complexation, a method also used in the CUR formulation Meriva [184]. Selecting appropriate indications and dosing strategies can also be helpful. One drug with low bioavailability that is already on the market is cannabidiol (CBD, Epidiolex). Researchers have developed precise dosing guidelines for CBD, recommending its simultaneous administration with a high-fat/high-calorie meal to significantly increase the time to reach maximum concentration [188].

Having the desired biological activity for the specified indications is one of the most essential characteristics of a drug. In clinical trials for CBD, the therapeutic effects were remarkable, and its metabolite, 7-OH-CBD, also retains activity [188]. However, the multitarget nature of natural products is advantageous for system regulation but leads to unclear mechanisms and difficulty achieving clinical endpoints. Standardizing natural extracts and fixing the components known to contribute to the main activity can significantly enhance drug efficacy, as demonstrated by the Eurosil 85 formulation mentioned previously [187].

A narrow therapeutic window makes the safety of some natural products unpredictable. Triptolide (TPL) demonstrates excellent anti-cancer activity but has significant toxicity and a narrow therapeutic window [189]. This has hindered the development of TPL as a systemic drug. Currently, TPL is mainly targeted to diseased tissues through methods such as encapsulation in nanoparticles, liposomes, or antibody-drug conjugates, reducing its toxicity to normal tissues [189]. Similar techniques have been successful in the commercialization of paclitaxel (PTX, Abraxane) [190]. In addition, CBD uses gradual dose escalation, which enables individualized treatment plans, maximizes the treatment window, and is also worthy of reference [188]. Some natural products, like BBR, have a wide therapeutic window and are mild metabolic regulators with no reported serious side effects [191]. As endogenous substances, MLT and similar natural products are highly safe, with even high doses well tolerated in the short term [192].

6. Conclusion and perspectives

Significant progress has been made in identifying natural products that target mitochondria. However, their multiple mechanisms, which simultaneously affect various mitochondrial functions pose challenges for defining their clinical applications. The regulation of OXPHOS and mitochondria-mediated apoptosis requires caution, as low-selectivity natural products risk causing systemic energy deficits or indiscriminate cell death. Modulating the mitochondrial quality control system provides organ-specific protection. In addition, the mechanisms of action of many natural products on mitochondria are not yet well understood. Future research should prioritize foundational studies on the intricate relationships between mitochondrial abnormalities and disease progression, deepening our understanding of mitochondrial physiology and laying a robust theoretical groundwork for innovative drug development.

With technological innovation, the study of natural products has become more convenient and efficient. Machine learning and other artificial intelligence-based screening methods excel at multitarget screening due to their powerful data processing and prediction capabilities [193]. While the natural origin makes many products unsustainable, synthetic biology offers a more sustainable and advantageous alternative. For example, synthesizing ginsenosides in yeast and the precursor of RSV in *Escherichia coli* makes natural products sustainable [194, 195]. Additionally, network pharmacology has helped elucidate the mechanisms of natural products by using databases such as SymMap, GeneCards, and STRING [196]. Multi-omics approaches are essential for precisely and efficiently discovering the targets and mechanisms of natural products. Single-cell metabolomics can identify cell subpopulations with greater precision and resolution, revealing the dynamic regulation of natural products across different cell groups and addressing the problem of scarce samples [197].

It is essential to improve the conversion of natural products into drugs. The commercialization of natural products faces numerous challenges, including low bioavailability, poor targeting selectivity, unstable pharmacokinetics, and a narrow therapeutic window. Addressing these issues requires targeted strategies.

In summary, this review summarizes disease-specific mitochondrial pathological phenotypes, natural products that address these phenotypes, and their mechanisms of action. It uniquely discusses obstacles in the drug development of natural products to advance mitochondria-targeted therapeutic strategies. However, this review has certain limitations. It does not provide a systematic comparison of the dosages and treatment durations for individual natural products across different disease models. Comparative studies remain scarce, and our analysis is necessarily limited to the most representative examples.

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Supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of Interest statement

The authors declare no competing financial interest.

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