Available online on 15.10.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Review Article

Molecular Mechanisms of Mitochondrial Dysfunction in Neurodegenerative Diseases: Pharmacological Targets and Therapeutic Advances

Nikita Patel [1], Trilochan Satapathy [1]*, Poonam Sahu [1], Abhisek Satapathy [2], Shiv Kumar Bhardwaj [1], Abinash Satapathy [4], Neha Yadav [4], Kunal Chandrakar [3], Manisha Chandrakar [3]

[1] Columbia Institute of Pharmacy, Vill-Tekari, Near Vidhansabha, Raipur-493111, C.G., India

[2] Pt J.N.M. Medical College, Railway Station Rd, Moudhapara, Raipur-492001, Chhattisgarh, India

[3] University College of Pharmacy, CSVTU, Bhilai, Durg-491107, Chhattisgarh, India

[4] College of Veterinary Science and Animal Husbandry, Anjora, Durg, 491001, C.G, India

Article Info:

Article History:

Received 21 July 2025
Reviewed 10 Sep 2025
Accepted 27 Sep 2025
Published 15 Oct 2025

Cite this article as:

Patel N, Satapathy T, Sahu P, Satapathy A, Bhardwaj SK, Satapathy A, Yadav N, Chandrakar K, Chandrakar M, Molecular Mechanisms of Mitochondrial Dysfunction in Neurodegenerative Diseases: Pharmacological Targets and Therapeutic Advances, Journal of Drug Delivery and Therapeutics. 2025; 15(10):272-294

DOI: http://dx.doi.org/10.22270/jddt.v15i10.7424

Abstract

One of the main characteristics of severe neurodegenerative disorders like amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD) is mitochondrial dysfunction. These disorders cause progressive neuronal degeneration due to abnormalities in mitochondrial energy metabolism, redox regulation, calcium homeostasis, and quality control pathways. Mechanistically, the key pathogenic causes are altered electron transport chain activity, dysregulated mitochondrial dynamics (fission and fusion), impaired mitophagy, and increased formation of reactive oxygen species (ROS). Furthermore, mutations in proteins such as PINK1, Parkin, SOD1, TDP-43, and huntingtin worsen mitochondrial instability and interfere with mitochondrial-nucleus communication.This review provides a comprehensive analysis of mitochondrial dysfunction from a mechanistic perspective, highlighting disease-specific pathways and molecular targets. We evaluate current and emerging pharmacological strategies, including mitochondria-targeted antioxidants, biogenesis activators, calcium modulators, and mitophagy enhancers. In addition, we discuss drug delivery innovations, such as mitochondrial-penetrating peptides and nanoparticle systems, as well as the clinical progress and limitations of mitochondrial therapies.By integrating insights from molecular biology, pharmacology, and translational neuroscience, this review outlines the therapeutic potential of targeting mitochondria and offers perspectives on future drug discovery aimed at mitigating neurodegeneration through mitochondrial repair and protection.

Keywords: Mitochondrial dysfunction, neurodegenerative diseases, PINK1, Parkinson's disease, Alzheimer's disease, SIRT3

*For Correspondence: Dr. Trilochan Satapathy, Professor and HOD, Columbia Institute of Pharmacy, Vill-Tekari, Near Vidhansabha, Raipur-493111, C.G., India

Highlights:

- Mitochondrial dysfunction is a convergent driver of Alzheimer's, Parkinson's, Huntington's, and ALS, linking bio-energetic failure, ROS overload, calcium imbalance, and impaired quality control.
- Distinct molecular defects-including Aβ-ABAD and tau interactions in AD, PINK1-Parkin mitophagy loss in PD, PGC-1α suppression in HD, and SOD1/TDP-43 mislocalization in ALS define disease-specific vulnerabilities.
- Therapeutic strategies under investigation restore bioenergetics, enhance mitophagy and NAD^+ metabolism, reduce oxidative stress, and prevent calcium-driven mPTP opening.
- Next-generation approaches leverage transcriptional activators, mitochondria-targeted delivery systems, and optically controlled therapeutics for precise mitochondrial modulation.
- Future directions emphasize genome editing, polypharmacology, patient-derived organoid/iPSC models, and AI-enabled drug discovery to accelerate mitochondrial-based interventions.

1. Introduction

Mitochondrial dysfunction constitutes a fundamental pathological hallmark across diverse neurodegenerative disorders, encompassing a wide array of structural, functional, and dynamic impairments. [1] Within the central nervous system (CNS), mitochondria play a pivotal role in sustaining neuronal viability by driving

ATP synthesis via oxidative phosphorylation, regulating calcium balance, modulating apoptotic cascades, and maintaining redox homeostasis[2]. Because neurons are highly specialized and energy-intensive, they are particularly susceptible to even subtle mitochondrial perturbations. [3] Disruptions arising from genetic defects, environmental exposures, or age-associated decline can lead to bio-energetic insufficiency, oxidative stress, impaired synaptic transmission, and activation of cell death pathways.[4] These alterations critically contribute to the onset and progression of major neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis. Common mitochondrial abnormalities reported in these conditions include reduced electron transport chain activity, mitochondrial DNA (mtDNA) mutations, excessive fragmentation, and defective trafficking and turnover.[5] Owing to their central involvement in neuronal function and survival, mitochondria are increasingly recognized as attractive therapeutic targets.[6] Advancing our understanding of the molecular mechanisms underlying mitochondrial dysfunction may pave the way for novel interventions aimed at restoring mitochondrial integrity, enhancing neuronal resilience, and modifying disease trajectory.[7]

1.1 Role of mitochondria in neuronal survival and plasticity

Mitochondria are integral to neuronal survival and neuroplasticity, the fundamental process by which the brain adapts structurally and functionally to internal and external cues.[8] Owing to their exceptionally high energy demands, neurons depend on mitochondrial activity to sustain ion gradients, propagate action potentials, and support neurotransmitter release and recycling. Through oxidative phosphorylation, mitochondria supply the bulk of cellular ATP required for these processes.[9] In addition to their bio-energetic role, mitochondria regulate intracellular calcium levels, thereby influencing synaptic transmission and signaling pathways associated with plasticity.[10] They further serve as both generators and regulators of reactive oxygen species (ROS), maintaining redox balance within the neuronal environment.[11] Mitochondrial quality control mechanisms-encompassing fission, fusion, biogenesis, and mitophagy are critical for distributing functional mitochondria to active synapses while eliminating damaged organelles. Disturbances in these processes compromise synaptic plasticity, reduce dendritic complexity, and heighten neuronal vulnerability, features commonly associated with neurodegenerative and psychiatric disorders.[12] Thus, mitochondrial integrity is not only vital for neuronal viability but also for sustaining the adaptive mechanisms that underlie learning, memory, and cognitive resilience.[13]

1.2 Brief overview of mitochondrial- targeted therapies:

Mitochondria-targeted therapeutic strategies have gained considerable attention as potential interventions for neurodegenerative disorders, owing to the pivotal contribution of mitochondrial dysfunction to neuronal loss.[14] Current approaches encompass the use of antioxidants such as MitoQ and Coenzyme Q10, pharmacological modulators of mitochondrial dynamics, agents that stimulate mitophagy, and compounds designed to enhance mitochondrial biogenesis or optimize electron transport chain activity.[15]Although these modalities have demonstrated promising outcomes in preclinical studies, their clinical translation remains constrained. A key limitation lies in the development of pharmacological agents capable of efficiently crossing the blood–brain barrier and accumulating within neuronal mitochondria at therapeutically relevant concentrations. Furthermore, the absence of reliable biomarkers to assess mitochondrial function in vivo hampers the real-time evaluation of treatment efficacy.[16] Disease heterogeneity, regional variability of mitochondrial involvement, and stage-specific pathological changes further complicate therapeutic design and evaluation.[17] Addressing these translational barriers will require the advancement of targeted delivery platforms, refined patient stratification strategies, and integrated biomarker frameworks.[18] Such progress is critical to fully harness the therapeutic potential of mitochondria-directed interventions in neurodegenerative disease management.[19]

2. Mitochondrial Physiology and Neuronal Function

2.1 Mitochondrial Bioenergetics

Electron transport chain (ETC) complexes I–V: structure and function

Five multi-subunit protein complexes (I-V) make up the electron transport chain (ETC), which is found in the inner mitochondrial membrane and is essential for oxidative phosphorylation and ATP synthesis.[20] Every complex plays a distinct part in the creation of the proton gradient that propels ATP production as well as the sequential transfer of electrons.[21]

Complex I: With more than 40 subunits, complex I is the biggest and most complicated ETC complex.[22] It speeds up the conversion of electrons from NADH to ubiquinone (coenzyme Q10) and the migration of four protons from the mitochondrial matrix into the intermembrane gap.[23] This proton pumping is one of the primary sources of the electrochemical gradient needed to produce ATP.[25]

Complex II: Complex II, a smaller complex that is involved in the citric acid cycle and the ETC, is also referred to as succinate dehydrogenase.[26] It contributes indirectly to the proton gradient because, in contrast to other complexes, it does not pump protons across the membrane; instead, it uses FADH2 to transport electrons from succinate to ubiquinone.[27]

Complex III: This complex uses a process called the Q-cycle to move electrons from reduced ubiquinone (ubiquinol) to cytochrome c.[28] Four protons are moved into the intermembrane gap during this procedure, which increases the proton motive force.[29] The Rieske iron-sulfur protein, cytochrome b, and cytochrome c1 are among the 11 subunits that make up Complex III.[30]

Complex IV: Complex IV, also known as cytochrome c oxidase, accepts electrons from cytochrome c and delivers them to molecular oxygen, the terminal electron acceptor, resulting in the formation of water.[31]This electron transfer process is tightly coupled to the translocation of two protons across the inner mitochondrial membrane per electron pair, thereby contributing to the maintenance of the proton motive force.[32]Structurally, Complex IV is composed of 13 subunits and incorporates critical copper and heme prosthetic groups that mediate efficient electron transfer and catalyze oxygen reduction.[33]

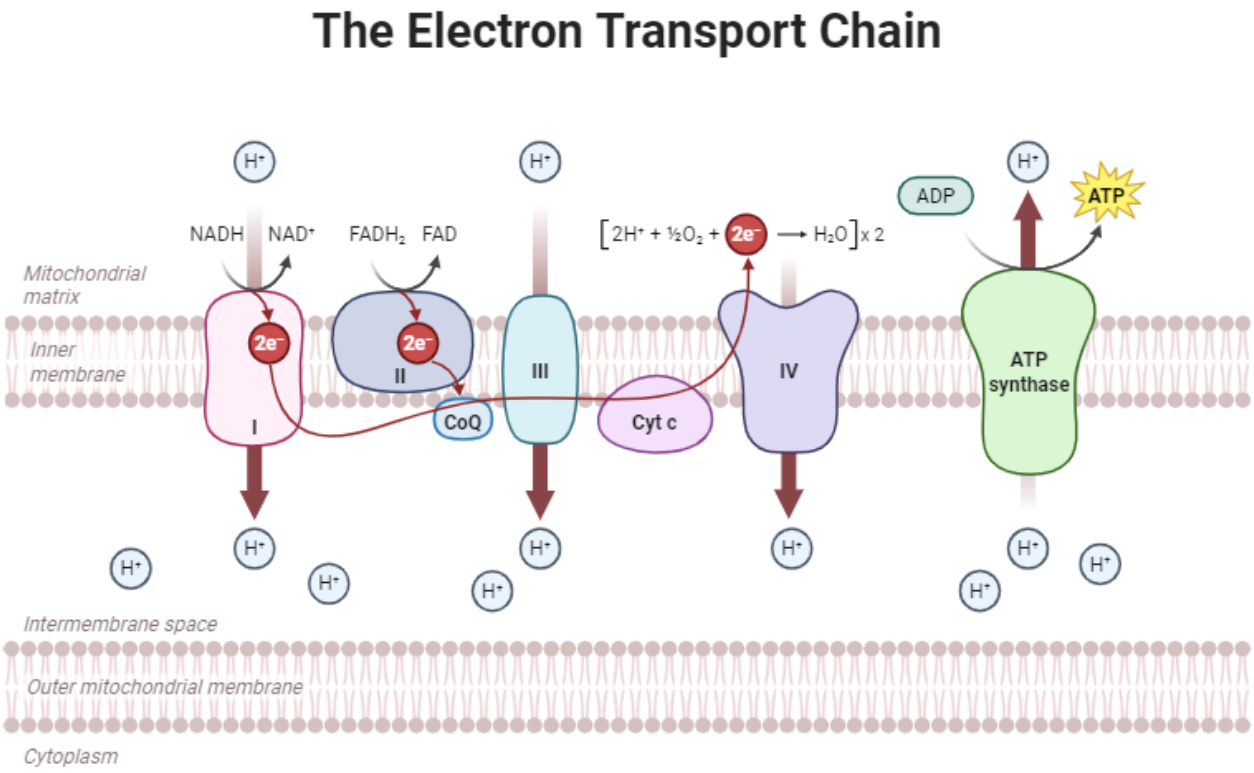

Figure 1: Graphical representation of Electron transport chain. Shows Inter- membrane space, inner membrane and matrix areas Illustration.

Complex V: Complex V, often referred to as F_0F_1-ATP synthase, uses the proton gradient produced by the other complexes to create ATP from inorganic phosphate and ADP.[34] Through the F_0 subunit, protons return to the matrix, causing the F_1 subunit's rotating mechanism to catalyse the production of ATP.[35] It is a highly conserved and dynamic complex essential for cellular energy production.Collectively, the five complexes of the electron transport chain function as a highly coordinated and interdependent system, wherein dysfunction at any stage can impair ATP production and threaten cellular survival. Such deficits are especially deleterious in metabolically demanding tissues, such as the brain, where energy homeostasis is critical for neuronal function and viability.[36]

2.1.1 ATP synthesis via oxidative phosphorylation (OXPHOS)

Oxidative phosphorylation (OXPHOS) within the inner mitochondrial membrane represents the terminal and most vital phase of cellular energy generation.[37]This process is driven by the sequential transfer of electrons through the electron transport chain (ETC), wherein reducing equivalents from NADH and $FADH_2$ are delivered to complexes I-IV, culminating in the reduction of molecular oxygen to water.[38] Electron flow is coupled to the translocation of protons from the mitochondrial matrix into the intermembrane space, thereby establishing an electrochemical gradient, or proton motive force. The stored potential energy of this gradient is subsequently utilized by Complex V (ATP synthase), which, upon proton re-entry into the matrix, undergoes conformational transitions that catalyze the phosphorylation of ADP to ATP. [39]This highly coordinated mechanism secures a sustained supply of ATP, indispensable for diverse cellular functions, particularly within neurons that demand substantial energy for synaptic activity and signaling.[40] Perturbations in OXPHOS not only compromise ATP production but also promote excessive reactive oxygen species (ROS) accumulation and cellular stress, processes that significantly contribute to the development and progression of neurodegenerative disorders.[41]

2.1.2 Role of mitochondrial membrane potential (ΔΨm)

The mitochondrial membrane potential (ΔΨm) is an electrochemical gradient across the inner mitochondrial membrane, generated by proton pumping through ETC complexes I, III, and IV. It represents the electrical component of the proton motive force that drives ATP synthesis via ATP synthase and also supports calcium uptake, metabolite transport, protein import, and

mitochondrial dynamics.[42] A stable ΔΨm reflects healthy mitochondrial function, whereas its loss is an early indicator of dysfunction and stress.[43] Sustained depolarization can induce mitochondrial permeability transition pore (mPTP) opening, release of cytochrome c, and activation of intrinsic apoptosis.[44] In neurons, where energy demand is high, even subtle disturbances in ΔΨm impair synaptic activity and plasticity, thereby contributing to neurodegeneration.[45]

2.2 Mitochondrial Dynamics

2.2.1 Fission and Fusion: Roles of Drp1, Fis1 (fission); Mfn1/2, OPA1 (fusion)

Mitochondrial dynamics, governed by the opposing processes of fission and fusion, are essential for maintaining organelle function, distribution, and quality control in energy-demanding cells such as neurons.[46] Fission is mediated by the recruitment of Drp1 to the outer mitochondrial membrane, where it oligomerizes and constricts the membrane with the aid of receptor proteins like Fis1, enabling organelle division and the removal of damaged fragments via mitophagy.[47]Fusion, in contrast, supports mitochondrial DNA integrity, metabolic cooperation, and stress adaptation.[48]This process involves Mitofusins (Mfn1/2) on the outer membrane and OPA1 on the inner membrane, which together facilitates membrane merging and preserves cristae structure.[49]Balanced fission and fusion allow mitochondria to adapt to metabolic demands and safeguard neuronal health.[50] Dysregulation-such as Drp1 overactivation or mutations in Mfn2 or OPA1-leads to abnormal morphology, impaired bioenergetics, and apoptosis, contributing to neurodegenerative diseases including Alzheimer's, Parkinson's, and Charcot-Marie-Tooth disease.[51]

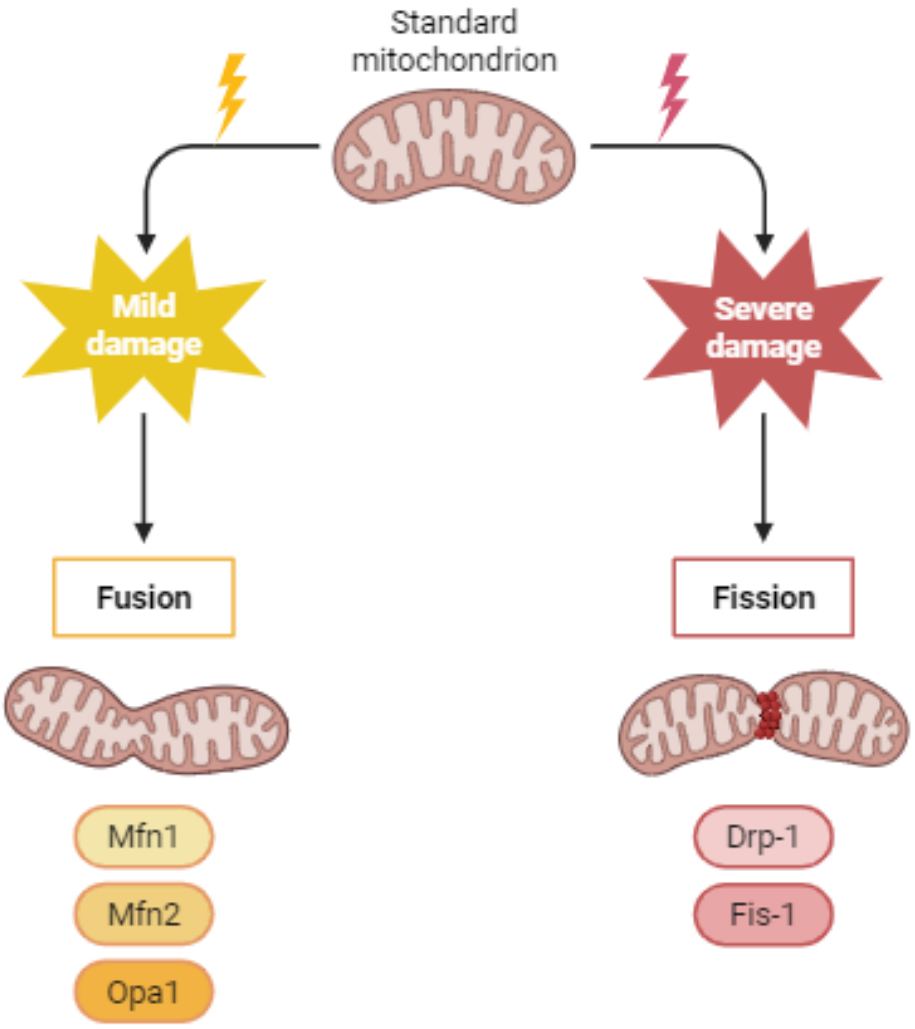

Figure 2: Mitochondrial fission and fusion.

2.2.2 Mitophagy: A specific type of autophagy called mitophagy removes damaged mitochondria to preserve cellular homeostasis, especially in neurons. The PINK1-Parkin pathway is the best-characterized mechanism, where loss of mitochondrial membrane potential leads to PINK1 accumulation on the outer membrane and activation of the E3 ligase Parkin.[52]Parkin ubiquitinates outer membrane proteins, which are then recognized by autophagy receptors linking mitochondria to LC3-positive autophagosomes. Fusion with lysosomes enables degradation of mitochondrial cargo, preventing oxidative stress and apoptosis.[53]Dysregulation of this pathway, especially through PINK1 or Parkin mutations,

contributes to neurodegenerative diseases such as Parkinson's disease.[54]

2.2.3 Mitochondrial trafficking: Mitochondrial trafficking in neurons is a tightly regulated process that ensures proper distribution of mitochondria to sites of elevated energy demand, such as synapses, while also facilitating the removal of damaged organelles to preserve cellular integrity.[55]Due to the long and complex structure of axons, this movement depends on active transport along microtubules mediated by molecular motors. Kinesins, particularly Kinesin-1, drive anterograde transport from the soma toward axon terminals, whereas dynein motors mediate retrograde movement, returning aged or dysfunctional mitochondria to the cell body for repair or degradation through mitophagy.[56] The linkage between mitochondria and these motors is established by adaptor proteins including TRAK1/2 (Milton) and the calcium-sensitive GTPase Miro, which regulate motor recruitment and activity. Through this machinery, mitochondria are efficiently positioned at synaptic regions to provide ATP and buffer calcium essential for neurotransmission and plasticity.[57] The balance between forward and backward trafficking is modulated by intracellular cues such as calcium concentration and metabolic state, allowing dynamic adaptation to neuronal demands.[58] Disruption of this transport system-caused by mutations in motors, adaptors, or regulatory proteins-results in mis-localization of mitochondria, impaired energy supply, and contributes to neurodegenerative pathologies including Alzheimer's disease and Charcot-Marie-Tooth disease.[59]

2.3 Calcium Homeostasis and ROS Regulation

2.3.1 Mitochondrial calcium uniporter (MCU) complex

Mitochondria act as central regulators of intracellular calcium (Ca^{2+}) dynamics and reactive oxygen species (ROS) balance, two processes that are tightly interconnected and fundamental for neuronal survival and function.[60] Calcium entry into the mitochondrial matrix is primarily mediated by the mitochondrial calcium uniporter (MCU) complex, located in the inner mitochondrial membrane.[61] The channel consists of the pore-forming MCU and regulatory subunits such as MICU1, MICU2, and EMRE, which together ensure precise control of Ca^{2+} uptake. Under basal conditions, MICU1 and MICU2 restrict calcium influx, thereby preventing mitochondrial overload.[62] During neuronal activity, elevations in cytosolic Ca^{2+} relieve this inhibition, allowing the MCU complex to rapidly import calcium, driven by the mitochondrial membrane potential.[63] This influx activates key dehydrogenases of the tricarboxylic acid (TCA) cycle, enhances NADH generation, and supports oxidative phosphorylation to meet acute energy demands.[64] While physiological calcium uptake promotes metabolic adaptation, excessive accumulation disrupts mitochondrial function by collapsing membrane potential ($\Delta\Psi m$), opening the mitochondrial permeability transition pore (mPTP), and triggering release of pro-apoptotic factors.[65] Calcium overload also enhances ROS production, particularly at complexes I and III of the electron transport chain, where electron leakage leads to superoxide formation. Although ROS at moderate levels act as signaling molecules, uncontrolled accumulation damages mitochondrial DNA, proteins, and lipids, propagating oxidative stress and neuronal injury.[66] To mitigate this, mitochondria deploy antioxidant systems such as manganese superoxide dismutase (MnSOD) and glutathione peroxidase, which maintain redox equilibrium.Dysregulation of MCU activity-arising from genetic mutations or pathological stress-disturbs calcium handling, compromises ATP synthesis, and intensifies oxidative stress, ultimately activating cell death pathways.[67] Such defects in calcium and ROS homeostasis are strongly implicated in neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, underscoring the MCU complex as a pivotal hub connecting calcium signaling with mitochondrial metabolism and redox control in neurons.[68]

2.3.2 Calcium buffering and crosstalk with endoplasmic reticulum (MAMs)

Mitochondria-associated membranes (MAMs) are specialized contact sites between the endoplasmic reticulum (ER) and mitochondria that play a central role in neuronal calcium signaling and homeostasis.[69] At these junctions, calcium released from ER stores via IP3Rs and RyRs is rapidly taken up by the mitochondrial calcium uniporter (MCU), creating localized microdomains that support efficient buffering and stimulate ATP production.[70] Tethering proteins such as Mitofusin 2, along with complexes involving IP3R-Grp75-VDAC, stabilize ER-mitochondria interactions and regulate calcium flux. By coordinating calcium transfer, MAMs link energy metabolism, apoptosis, and autophagy to neuronal signaling demands.[71]Impairment of MAM function disrupts calcium handling and has been implicated in neurodegenerative diseases including Alzheimer's and Parkinson's.[72]

2.3.3 ROS production sites in ETC (mainly complexes I and III)

Mitochondrial ROS are mainly generated at Complexes I and III of the electron transport chain, where electron leakage leads to superoxide formation.[73] At Complex I, impaired electron flow or reverse electron transport promotes premature oxygen reduction at FMN or Fe-S centers, while at Complex III, semiquinone intermediates formed during the Q-cycle leak electrons at the Qo site.[74] Superoxide is rapidly converted to hydrogen peroxide, which serves as a signaling molecule at physiological levels but induces oxidative damage when overproduced. Excessive ROS impairs mitochondrial DNA, lipids, and respiratory proteins, creating a vicious cycle of dysfunction.[75] Such oxidative stress contributes to neurodegenerative disorders, notably Parkinson's and Alzheimer's disease, making Complexes I and III critical therapeutic targets.[76]

3. Disease-Specific Molecular Mechanisms of Mitochondrial Dysfunction

3.1 Alzheimer's Disease (AD)

Aβ-induced mitochondrial toxicity: Aβ binding alcohol dehydrogenase (ABAD): In Alzheimer's disease (AD), amyloid-β (Aβ) peptides not only form extracellular plaques but also accumulate within mitochondria, where they interact with amyloid-β binding alcohol dehydrogenase (ABAD).[77]This binding alters ABAD function, disrupts metabolic processes, and promotes excessive reactive oxygen species (ROS) production, leading to oxidative damage of mitochondrial DNA, lipids, and respiratory proteins.[78] The Aβ-ABAD interaction also impairs calcium buffering, destabilizes mitochondrial membrane potential, and triggers permeability transition pore opening, facilitating apoptotic signaling.[79] These combined effects compromise mitochondrial bioenergetics and contribute to neuronal loss and cognitive decline in AD.[80] Blocking the Aβ-ABAD interaction has been shown to restore mitochondrial function, underscoring its significance as a therapeutic target.[81]

Interaction of Aβ with mitochondrial import machinery (TOM/TIM): In Alzheimer's disease (AD), amyloid-β (Aβ) peptides accumulate in mitochondria and disrupt the protein import machinery governed by the TOM and TIM complexes.[82] By binding to TOM components such as TOM20 and TOM40, Aβ impairs recognition and translocation of precursor proteins, while also interfering with TIM-mediated passage into the inner membrane and matrix.[83] This blockade reduces the import of essential enzymes and structural proteins, weakening the electron transport chain, ATP production, and mitochondrial proteostasis.[84] Additionally, Aβ accumulation in import channels promotes membrane potential dissipation and excessive reactive oxygen species (ROS) generation.[85]These combined defects drive mitochondrial dysfunction, oxidative stress, and neuronal loss, identifying protein import pathways as potential therapeutic targets in AD.[86]

Tau-mediated disruption of mitochondrial trafficking: Tau, a microtubule-associated protein crucial for stabilizing neuronal microtubules, is essential for maintaining proper mitochondrial trafficking.[87] In Alzheimer's disease and other tauopathies, hyperphosphorylated Tau dissociates from microtubules and aggregates, destabilizing the cytoskeletal network required for axonal transport.[88] This disruption interferes with kinesin- and dynein-driven mitochondrial motility, partly through abnormal interactions with motor-adaptor complexes such as Milton/TRAK and Miro.[89] As a result, mitochondria become mislocalized, accumulating in the soma and failing to reach distal synapses, while damaged mitochondria are inefficiently removed.[90]These defects compromise energy supply, calcium buffering, and redox homeostasis, thereby driving synaptic dysfunction and neurodegeneration.[91]

Mitochondrial fission/fusion imbalance and decreased Complex IV activity: Mitochondrial dynamics, governed by the balance between fission and fusion, are essential for maintaining organelle integrity, energy production, and neuronal function.[92] In neurodegenerative diseases, excessive Drp1-mediated fission and reduced Mfn1/2- and OPA1-driven fusion promote mitochondrial fragmentation, impairing cristae structure and destabilizing respiratory supercomplexes, particularly Complex IV. Loss of Complex IV efficiency disrupts electron transfer, enhances ROS generation, and accelerates oxidative damage to mitochondrial DNA, proteins, and lipids.[93] Fragmented mitochondria also fail to undergo compensatory fusion, leading to accumulation of defective organelles.[94] This interplay between disrupted dynamics and Complex IV dysfunction drives energy deficits and oxidative stress, contributing to neuronal degeneration in Alzheimer's and Parkinson's disease.[95]

3.2 Parkinson's Disease (PD)

In Parkinson's disease (PD), loss-of-function mutations in PINK1 and Parkin disrupt mitophagy, the selective clearance of damaged mitochondria.[96] Normally, PINK1 accumulates on depolarized mitochondria, phosphorylates ubiquitin and Parkin, and facilitates Parkin-mediated ubiquitination of outer membrane proteins, marking defective organelles for autophagic degradation.[97] Mutations in either protein impair this pathway, leading to persistence of dysfunctional mitochondria with reduced ATP production, excessive ROS generation, and release of pro-apoptotic factors.[98] The accumulation of damaged mitochondria promotes dopaminergic neuronal loss in the substantia nigra and drives neuroinflammation, highlighting PINK1-Parkin-mediated mitophagy as a central mechanism of mitochondrial quality control and a critical contributor to PD pathogenesis.[99]

α-Synuclein aggregation impairing mitochondrial protein import: In Parkinson's disease and related synucleinopathies, aggregated α-synuclein contributes to mitochondrial dysfunction by disrupting the protein import machinery.[100] Misfolded α-synuclein oligomers and fibrils aberrantly localize to mitochondria, where they bind to TOM20 and impair the recognition and translocation of nuclear-encoded precursor proteins.[101] This blockade reduces import of essential respiratory and maintenance proteins, leading to defective electron transport chain function, diminished ATP synthesis, and increased ROS generation.[102] The failure to import protective enzymes further exacerbates oxidative stress, creating a self-reinforcing cycle of mitochondrial damage that drives neuronal energy failure and degeneration.[103]

Complex I inhibition by environmental toxins (e.g., MPTP): In Parkinson's disease (PD), the environmental toxin MPTP induces mitochondrial dysfunction by selectively inhibiting Complex I of the electron transport chain.[104] After crossing the blood-brain barrier, MPTP is metabolized to MPP^+, which is taken up by dopaminergic neurons via the dopamine transporter.[105] Within mitochondria, MPP^+ blocks electron transfer at

Complex I, reducing ATP synthesis and increasing ROS generation.[106] The resulting energy deficit and oxidative stress drive dopaminergic neuronal death in the substantia nigra, illustrating how environmental toxins mimic genetic mitochondrial defects and highlight the central role of Complex I vulnerability in PD pathogenesis.[107]

3.3 Huntington's Disease (HD)

Mutant huntingtin interaction with mitochondrial outer membrane: In Huntington's disease (HD), mutant huntingtin (mHTT) with expanded polyglutamine repeats disrupts mitochondrial function through direct interactions with outer membrane proteins.[108] Binding to voltage-dependent anion channels (VDACs) alters metabolite and calcium exchange, impairing ATP production, while interference with the TOM complex blocks import of essential nuclear-encoded proteins.[109] These defects reduce membrane potential, compromise respiratory chain activity, and elevate ROS production, leading to oxidative damage and release of pro-apoptotic factors.[110]Such mitochondrial dysfunction is particularly detrimental to striatal neurons, driving the progressive neurodegeneration characteristic of HD.[111]

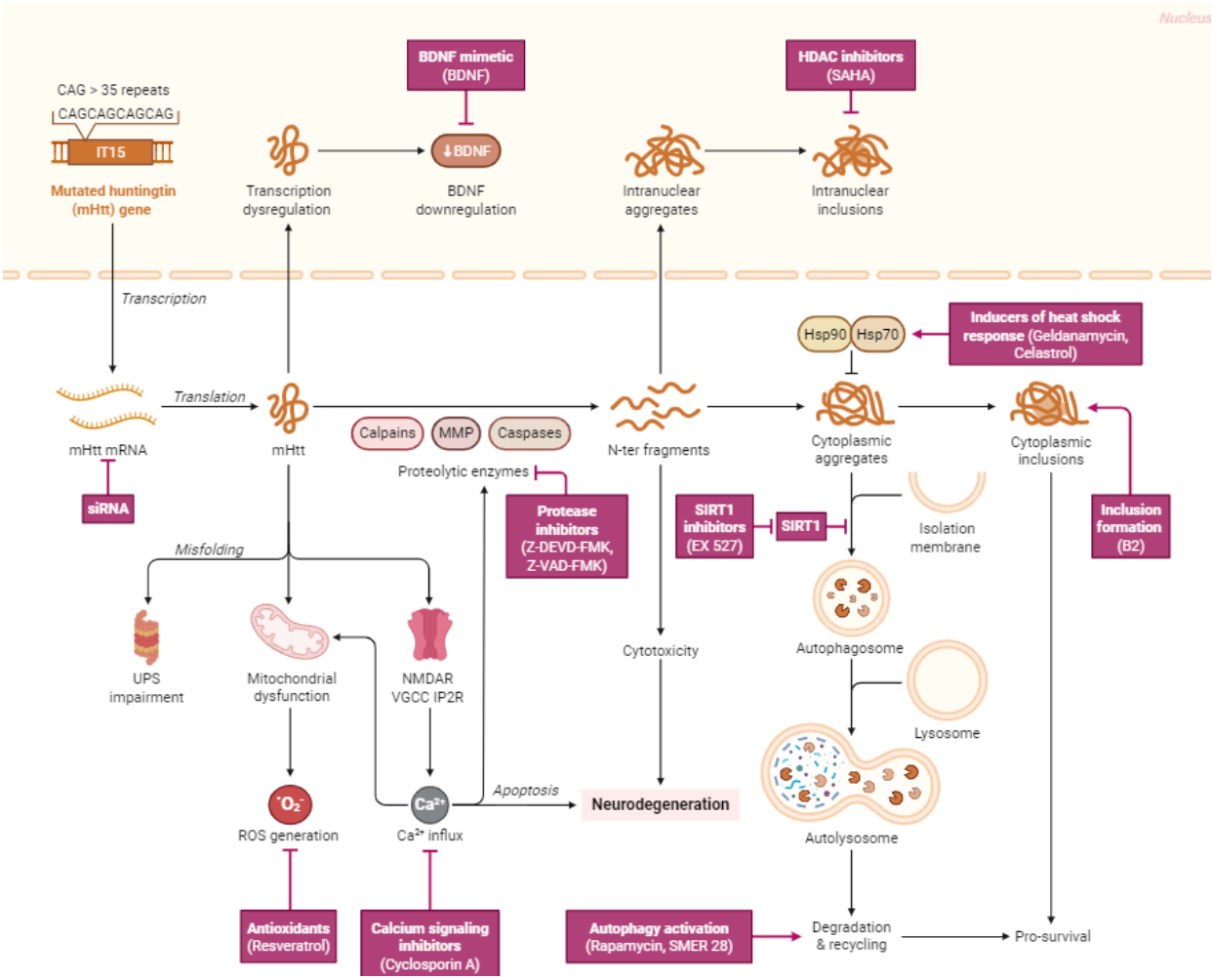

Figure 3: An overview of Huntington's Disease (HD)

Transcriptional repression of PGC-1α affecting biogenesis: Mitochondrial biogenesis, the process responsible for generating new mitochondria, is primarily controlled by the transcriptional co-activator PGC-1α (peroxisome proliferator-activated receptor gamma co-activator 1-alpha).[112] This regulator orchestrates the coordinated expression of nuclear and mitochondrial genes that sustain energy metabolism and respiratory efficiency.[113] In Huntington's disease (HD), the mutant huntingtin protein (mHTT) impairs this pathway by suppressing PGC-1α transcription.[114] Mechanistically, mHTT interferes with regulatory elements of PGC-1α, including transcription factors such as CREB (cAMP response element-binding protein) and cofactors like TAF4 (TATA-binding protein-associated factor 4), either by sequestering them or disrupting their functional activity.[115] This leads to downregulation of PGC-1α, which in turn compromises the activation of nuclear respiratory factors (NRF-1 and NRF-2) and mitochondrial transcription factor A (TFAM), both indispensable for mitochondrial DNA replication and transcription.[116] The decline in PGC-1α activity ultimately suppresses mitochondrial biogenesis, reflected by decreased mitochondrial content, improper assembly of respiratory chain complexes, and reduced ATP generation. Additionally, reduced PGC-1α signaling diminishes antioxidant defense enzyme expression, intensifying oxidative stress and mitochondrial injury.[117] Collectively, these defects produce severe energy shortages and heighten neuronal susceptibility to

excitotoxic and metabolic insults, thereby driving the progressive neurodegeneration characteristic of HD.[118]

Increased susceptibility to Ca^{2+}-induced mitochondrial permeability transition: In Parkinson's disease (PD), a major driver of mitochondrial dysfunction and neuronal loss is the increased susceptibility of mitochondria to calcium (Ca^{2+})-induced permeability transition.[119] Normally, mitochondria regulate Ca^{2+} uptake in a controlled manner to support ATP generation and intracellular signaling. In PD, however, genetic defects (including mutations in PINK1, Parkin, and DJ-1) and environmental toxins disrupt this balance, resulting in pathological accumulation of Ca^{2+} within the mitochondrial matrix.[120] Excess matrix Ca^{2+} serves as a potent trigger for opening of the mitochondrial permeability transition pore (mPTP), a high-conductance channel located in the inner mitochondrial membrane.[121] The pore is thought to be formed through interactions of adenine nucleotide translocase (ANT), cyclophilin D (CypD), and the phosphate carrier, which become destabilized under Ca^{2+} overload. mPTP opening leads to a rapid collapse of mitochondrial membrane potential ($\Delta\Psi m$), inhibition of oxidative phosphorylation, and failure of ATP production.[122] Furthermore, it permits the release of apoptogenic proteins such as cytochrome c into the cytoplasm, thereby activating programmed cell death pathways.[123] Oxidative stress and elevated reactive oxygen species (ROS), both prominent in PD, further sensitize mPTP components by oxidizing critical thiol residues, intensifying mitochondrial swelling and membrane rupture. Collectively, Ca^{2+}-driven mPTP opening contributes to energy failure and apoptotic signaling, particularly in dopaminergic neurons of the substantia nigra, which are inherently vulnerable. This mechanism is central to the progressive neurodegeneration that characterizes Parkinson's disease.[124]

3.4 Amyotrophic Lateral Sclerosis (ALS)

3.4.1 Mutant SOD1 localization to mitochondria: oxidative stress and swelling

In ALS, mutant SOD1 misfolds and abnormally accumulates in mitochondria, where it binds to outer membrane proteins such as VDACs and disrupts protein import and ion exchange. This mislocalization impairs ROS detoxification, leading to superoxide buildup, oxidative damage to mitochondrial components, and defective electron transport chain activity.[125] Excess ROS and calcium overload trigger opening of the mitochondrial permeability transition pore (mPTP), causing loss of membrane potential, mitochondrial swelling, and release of cytochrome c. These events activate apoptotic pathways, and due to their high energy demand and low antioxidant capacity, motor neurons are especially vulnerable, culminating in their degeneration.[126]

3.4.2 TDP-43 and FUS mislocalization disrupting mitochondrial transcriptome

In ALS and FTD, the RNA-binding proteins TDP-43 and FUS mislocalize from the nucleus to the cytoplasm and mitochondria, where they aberrantly bind mitochondrial transcripts and RNA-processing machinery.[127] This disrupts mitochondrial RNA splicing, polyadenylation, and stability, leading to reduced synthesis of essential electron transport chain subunits. Consequently, oxidative phosphorylation is impaired, ATP production declines, and electron leakage increases, driving ROS accumulation and oxidative stress. These mitochondrial defects also disturb dynamics and quality control, resulting in fragmentation and dysfunction that heighten neuronal vulnerability and contribute to progressive neurodegeneration.[128]

3.4.3 Disrupted ER-mitochondrial tethering and calcium dysregulation

Mitochondria-associated membranes (MAMs) are specialized ER–mitochondria contact sites that coordinate calcium (Ca^{2+}) signaling and cellular metabolism. Through IP3Rs on the ER, VDACs on the mitochondrial outer membrane, and bridging proteins such as mitofusin-2 (Mfn2), these sites enable efficient Ca^{2+} transfer to mitochondria, stimulating ATP production via activation of TCA cycle dehydrogenases.[129] In neurodegenerative diseases like Alzheimer's and Parkinson's, disruption of MAM integrity-due to altered Mfn2 expression or impaired IP3R–VDAC interactions-reduces mitochondrial Ca^{2+} uptake, leading to energy deficits, cytosolic Ca^{2+} overload, oxidative stress, and apoptosis.[130] Additionally, impaired tethering perturbs lipid metabolism and autophagy, further destabilizing mitochondrial function. Collectively, ER–mitochondrial uncoupling and Ca^{2+} dysregulation emerge as central mechanisms driving mitochondrial dysfunction and neuronal loss in CNS disorders.[131]

4. Pharmacological Modulation of Mitochondrial Targets

4.1 Enhancing Mitochondrial Bioenergetics

Creatine: Creatine is an endogenous nitrogen-containing metabolite that plays a pivotal role in sustaining cellular energy balance by serving as a readily available phosphate donor for rapid ATP regeneration. The creatine kinase system, located in both the cytosol and mitochondria, catalyzes the reversible transfer of a high-energy phosphate group from ATP to creatine, producing phosphocreatine.[132] This high-energy compound functions as a dynamic reservoir and buffering system for ATP, ensuring stable energy supply during fluctuating metabolic demands, particularly in energy-intensive cells such as neurons and myocytes. By safeguarding ATP availability, creatine contributes to the maintenance of mitochondrial bioenergetics, especially under conditions of metabolic stress or impaired oxidative phosphorylation.[133]In neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (ALS), mitochondrial dysfunction and energy insufficiency represent major pathogenic mechanisms underlying motor neuron loss. Owing to its role in energy homeostasis, creatine has been extensively explored as a potential therapeutic strategy aimed at augmenting mitochondrial function and

delaying neurodegeneration.[134] Preclinical investigations demonstrated neuroprotective properties of creatine through enhanced energy buffering capacity and attenuation of oxidative damage. However, clinical evaluations in ALS patients have yielded inconsistent results: while some trials reported modest improvements in functional outcomes, others observed negligible or no significant therapeutic benefit.[135] These discrepancies likely reflect challenges related to pharmacokinetics, optimal dosing regimens, and the multifaceted pathophysiology of ALS.Despite these limitations, creatine remains an important model compound emphasizing the therapeutic relevance of targeting mitochondrial energy metabolism in neurodegenerative disease management.[136]

Dichloroacetate (DCA): **promotes pyruvate dehydrogenase activity:** Dichloroacetate (DCA) is a small molecule known to modulate mitochondrial metabolism through activation of the pyruvate dehydrogenase complex (PDH), a key enzymatic system that bridges glycolysis with the tricarboxylic acid (TCA) cycle. Under physiological conditions, PDH facilitates the oxidative conversion of pyruvate into acetyl-CoA, thereby sustaining mitochondrial respiration and ATP synthesis.[137] Its activity, however, is negatively regulated by pyruvate dehydrogenase kinases (PDKs), which phosphorylate and inactivate PDH. In several neurodegenerative disorders and metabolic abnormalities, upregulated PDK activity results in excessive PDH inhibition, driving a pathological shift from oxidative phosphorylation toward anaerobic glycolysis and contributing to cellular energy deficits.[138]DCA counteracts this process by selectively inhibiting PDK isoforms, thereby preventing PDH phosphorylation and reactivating its catalytic function. This re-establishes the oxidative metabolism of pyruvate, increases acetyl-CoA entry into the TCA cycle, and enhances mitochondrial ATP production through improved coupling with the electron transport chain.[139] The metabolic reorientation toward oxidative phosphorylation also reduces lactate buildup and mitigates oxidative stress associated with impaired mitochondrial function.Experimental studies have demonstrated that DCA can restore mitochondrial bioenergetics and support neuronal survival in models of neurodegenerative diseases such as Parkinson's and Alzheimer's.[140] Ongoing clinical investigations continue to evaluate its therapeutic potential. Collectively, DCA represents a promising metabolic modulator that targets PDH activity to correct mitochondrial dysfunction and improve neuronal energy homeostasis.[141]

4.2 Antioxidant Therapies

MitoQ, SkQ1: **mitochondria-targeted antioxidants via triphenyl phosphonium cation**: MitoQ and SkQ1 are mitochondria-targeted antioxidants that accumulate within the mitochondrial matrix via the triphenyl phosphonium (TPP^+) cation, which exploits the highly negative membrane potential to achieve selective delivery. Once inside, MitoQ, a ubiquinone derivative, and SkQ1, containing plastoquinone, directly scavenge reactive oxygen species (ROS) at primary sites of production within the electron transport chain. By reducing oxidative damage to mitochondrial DNA, proteins, and lipids, and preventing lipid peroxidation in membranes, both compounds stabilize mitochondrial membrane potential, limit permeability transition pore opening, and preserve ATP synthesis.[142] These actions protect against neuronal apoptosis and bioenergetic failure. Preclinical studies demonstrate that MitoQ and SkQ1 mitigate oxidative stress, neuroinflammation, and cell death in models of Parkinson's and Alzheimer's diseases, highlighting their potential as neuroprotective agents targeting mitochondrial dysfunction.[143]

EPI-743: EPI-743 (vatiquinone) is a redox-active compound that enhances mitochondrial function by modulating intracellular NADPH-dependent antioxidant systems. It undergoes redox cycling through enzymes such as NQO1, thereby sustaining NADPH availability and promoting glutathione regeneration, which is essential for detoxifying reactive oxygen species and maintaining redox homeostasis.[144] In addition, EPI-743 can act as an alternative electron carrier, partially bypassing impaired components of the electron transport chain to improve mitochondrial bioenergetics.[145] Through these mechanisms, it reduces oxidative damage to mitochondrial macromolecules, preserves membrane potential, and prevents apoptosis. Preclinical and clinical studies in mitochondrial encephalopathies, including Leigh syndrome, indicate that EPI-743 supports neuronal survival and slows disease progression, highlighting its therapeutic promise in disorders driven by oxidative stress and energy failure.[146]

4.2.1 Limitations of non-targeted antioxidants (e.g., vitamin E, CoQ10)

Non-targeted antioxidants such as vitamin E and coenzyme Q10 (CoQ10) have been investigated for their ability to reduce oxidative stress in neurodegenerative diseases; however, their impact on mitochondrial dysfunction remains limited. Mitochondrial oxidative damage is primarily driven by reactive oxygen species generated at complexes I and III of the electron transport chain, requiring antioxidants to localize within the mitochondrial matrix or inner membrane to be effective.[147] Vitamin E, while lipid-soluble, distributes broadly across cellular membranes without mitochondrial specificity, restricting its capacity to neutralize intra-mitochondrial ROS.[148] Similarly, exogenous CoQ10 supplementation is hindered by poor bioavailability and limited incorporation into the inner mitochondrial membrane, despite being an endogenous ETC component. As a result, both compounds act diffusely, necessitating high doses that risk systemic side effects and interference with physiological ROS signaling essential for processes such as mitochondrial biogenesis and autophagy. Clinical outcomes with vitamin E and CoQ10 have been inconsistent, reflecting their poor mitochondrial targeting and the complex pathophysiology of neurodegeneration. Overall, the lack of precise mitochondrial delivery explains the limited

therapeutic efficacy of these non-targeted antioxidants in addressing mitochondrial oxidative stress.[149]

4.3 Mitophagy and Quality Control Enhancers

Urolithin A: Urolithin A is a natural metabolite that enhances mitochondrial quality control by promoting mitophagy, the selective clearance of damaged mitochondria.[150] Mechanistically, it activates the cellular energy sensor AMPK, which in turn phosphorylates ULK1 to initiate the autophagy cascade, leading to autophagosome formation and degradation of dysfunctional mitochondria.[151] This targeted removal prevents excessive reactive oxygen species production and preserves cellular homeostasis while simultaneously stimulating mitochondrial biogenesis to replenish healthy organelles.[152] Through this dual action of clearance and renewal, Urolithin A improves mitochondrial function, muscle performance, and cognitive outcomes in preclinical models of aging and disease.[153] By modulating the AMPK/ULK1 signaling axis to restore mitochondrial turnover, Urolithin A represents a promising therapeutic strategy for neurodegenerative disorders characterized by impaired mitophagy and energy failure.[154]

Nicotinamide riboside (NR) and **NMN**: Nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) are NAD^+ precursors that restore cellular NAD^+ pools depleted during aging and neurodegeneration. Once converted via the salvage pathway, elevated NAD^+ levels activate sirtuin deacetylases, particularly SIRT1 in the nucleus and SIRT3 in mitochondria. SIRT1 enhances mitochondrial biogenesis and antioxidant defenses by activating PGC-1α, while SIRT3 improves mitochondrial efficiency through deacetylation of enzymes in the electron transport chain, TCA cycle, and antioxidant systems. Together, these pathways reduce ROS production, support ATP synthesis, and maintain mitochondrial integrity. By rejuvenating mitochondrial metabolism and resilience, NR and NMN offer therapeutic potential in slowing neurodegenerative decline and promoting healthy aging.[155]

PARP inhibitors: Poly (ADP-ribose) polymerases (PARPs) are DNA repair enzymes that consume NAD^+ during PARylation in response to genotoxic stress.[156] Under chronic oxidative stress, excessive PARP activation depletes NAD^+, leading to impaired ATP production, mitochondrial dysfunction, and neuronal energy failure.[157] PARP inhibitors prevent this overconsumption of NAD^+, thereby preserving cellular bioenergetics, sustaining mitochondrial respiration, and reducing activation of cell death pathways such as parthanatos.[156] By maintaining NAD^+ availability, these inhibitors also support sirtuin activity, which promotes mitochondrial integrity and stress resistance.[159] In neurodegenerative conditions marked by persistent DNA damage and oxidative stress, PARP inhibition represents a targeted strategy to counteract NAD^+ loss, protect neuronal energy metabolism, and enhance cell survival.[160]

4.4 Inhibitors of mPTP and Calcium Dysregulation

Cyclosporin A: Cyclosporin A is a well-established pharmacological compound recognized for its protective actions on mitochondria, primarily through inhibition of cyclophilin D (CypD), a central regulator of the mitochondrial permeability transition pore (mPTP). The mPTP, a non-specific high-conductance channel within the inner mitochondrial membrane, becomes pathologically activated in response to calcium overload, oxidative stress, or excessive reactive oxygen species (ROS).[161] Its opening results in the dissipation of the mitochondrial membrane potential (ΔΨm), mitochondrial swelling, rupture of the outer membrane, and subsequent release of apoptogenic proteins such as cytochrome c, ultimately driving cell death.Cyclophilin D, a peptidyl-prolyl cis-trans isomerase, facilitates pore opening by increasing its sensitivity to calcium and redox alterations. Cyclosporin A binds with high affinity to CypD, thereby preventing its association with pore components and stabilizing the mPTP in a closed state. Through this mechanism, Cyclosporin A preserves ΔΨm, sustains ATP generation, and prevents the mitochondrial release of pro-apoptotic mediators despite the presence of damaging stimuli.At the cellular level, this action ensures maintenance of mitochondrial and cytosolic calcium homeostasis, counteracting calcium-driven mitochondrial swelling and dysfunction.[162] Such stabilization of mitochondrial bioenergetics and calcium regulation underlies the neuroprotective effects of Cyclosporin A in experimental models of ischemic injury and neurodegenerative disorders, where mPTP-dependent cell death is a key pathological feature. Thus, Cyclosporin A serves as a prototypical example of how targeting mitochondrial permeability transition regulators can protect against stress-induced cellular injury.[163]

Ru360: Ru360 is a selective inhibitor of the mitochondrial calcium uniporter (MCU), a channel complex located in the inner mitochondrial membrane that facilitates calcium (Ca^{2+}) transport from the cytosol into the mitochondrial matrix. Mechanistically, Ru360 binds to the pore-forming subunit of MCU, thereby obstructing Ca^{2+} entry and preventing mitochondrial calcium overload. Under physiological conditions, moderate mitochondrial Ca^{2+} uptake is essential for activating metabolic enzymes and supporting ATP synthesis; however, excessive accumulation triggers detrimental events such as mitochondrial permeability transition pore (mPTP) opening, dissipation of membrane potential, oxidative stress, and initiation of cell death pathways.By restricting Ca^{2+} influx, Ru360 safeguards mitochondria from calcium-induced swelling, excessive ROS generation, and bio-energetic collapse. In addition, this inhibition contributes to the maintenance of intracellular calcium balance, preserving cytosolic–mitochondrial signaling dynamics that are critical for cellular function. Owing to its specificity, Ru360 enables modulation of mitochondrial calcium handling without broadly interfering with calcium-dependent processes elsewhere in the cell.Through this targeted mechanism, Ru360 prevents calcium-driven mitochondrial dysfunction, a

pathological hallmark of ischemic injury and neurodegenerative diseases. Thus, Ru360 serves as a valuable experimental tool and highlights the therapeutic promise of MCU modulation in conditions where calcium dysregulation compromises mitochondrial integrity and neuronal viability.[164]

Dantrolene: Dantrolene acts as a selective antagonist of ryanodine receptors (RyRs), the intracellular calcium-release channels predominantly expressed on the endoplasmic reticulum (ER) membrane. RyRs are central regulators of intracellular calcium signaling, controlling the mobilization of Ca^{2+} from the ER into the cytosol. This process is especially critical at mitochondria-associated membranes (MAMs), where ER-mitochondria contacts allow direct transfer of Ca^{2+} into the mitochondrial matrix. Under pathological conditions, aberrant or excessive RyR activation promotes mitochondrial calcium overload, leading to dysfunction through mitochondrial permeability transition pore (mPTP) opening, reactive oxygen species (ROS) overproduction, dissipation of membrane potential, and initiation of apoptotic cascades.By binding to RyRs, Dantrolene stabilizes the channels in a less active conformation, thereby limiting ER Ca^{2+} release. This restriction reduces Ca^{2+} flux toward mitochondria, maintaining mitochondrial calcium homeostasis and protecting against swelling, bio-energetic collapse, and loss of membrane integrity. At the molecular level, Dantrolene helps preserve the finely tuned ER-mitochondria calcium signaling axis, which is essential for sustaining metabolism, ATP production, and cellular viability.In neurodegenerative contexts, where disrupted ER-mitochondrial calcium coupling is a major driver of neuronal injury, Dantrolene's modulation of RyR activity offers a protective strategy to prevent calcium-induced mitochondrial stress. Thus, by attenuating pathological ER-to-mitochondria calcium transfer, Dantrolene supports mitochondrial integrity and enhances neuronal survival.[165]

Table 1: Biogenesis Inducers and Transcriptional Activators

Biogenesis Inducer / Transcriptional Activator	Active Compound(s)	Mechanism / Effect
Bezafibrate	Fibric acid derivative (PPAR pan-agonist)	Activates PPARα/δ/γ → ↑ PGC-1α → promotes mitochondrial biogenesis, enhances fatty acid β-oxidation, improves oxidative phosphorylation.[166]
Pioglitazone	Thiazolidinedione (PPARγ agonist)	Activates PPARγ → upregulates PGC-1α and NRF1/2 → ↑ mitochondrial biogenesis, improves insulin sensitivity and lipid metabolism.[167]
Resveratrol	Polyphenolic compound (stilbene)	Activates SIRT1 and AMPK → deacetylates/activates PGC-1α → ↑ mitochondrial biogenesis, enhances oxidative metabolism, antioxidant defense.[168]

5. Molecular Targets in Drug Discovery and Development

5.1 High-throughput Screening Targets

Drp1 inhibitors (e.g., Mdivi-1)

Dynamin-related protein 1 (Drp1) is a GTPase that regulates mitochondrial fission, a process essential for maintaining mitochondrial quality and function. In neurodegenerative diseases, aberrant Drp1 activation promotes excessive mitochondrial fragmentation, leading to energy failure, oxidative stress, and neuronal loss. Normally cytosolic, Drp1 translocates to the mitochondrial outer membrane upon activation, where it interacts with receptors such as Fis1, Mff, MiD49, and MiD51 to drive scission.[169]The small molecule Mdivi-1 selectively inhibits Drp1 GTPase activity, preventing the conformational changes required for fission. By preserving mitochondrial network integrity, Mdivi-1 enhances membrane potential, ATP production, and reduces ROS, cytochrome c release, and apoptosis. Beyond stabilizing dynamics, Drp1 inhibition indirectly supports mitophagy and biogenesis, making compounds like Mdivi-1 attractive candidates for therapeutic development in disorders such as Parkinson's, Alzheimer's, and Huntington's disease.[170]

SIRT3 activators

SIRT3, a mitochondrial NAD^+-dependent deacetylase, has emerged as a promising target in mitochondrial drug discovery due to its pivotal role in metabolism, antioxidant defense, and cellular homeostasis. Residing in the mitochondrial matrix, SIRT3 activates key enzymes of fatty acid oxidation, the TCA cycle, and the electron transport chain, while also enhancing antioxidant defenses by deacetylating substrates such as SOD2 and IDH2.[171] Through these actions, SIRT3 improves oxidative phosphorylation, reduces ROS generation, and protects mitochondrial DNA and proteins from oxidative injury.High-throughput screening has identified small molecules capable of activating SIRT3, either directly or via NAD^+ modulation. Pharmacological enhancement of SIRT3 restores ATP production, maintains mitochondrial membrane potential, and mitigates oxidative stress-effects particularly relevant to aging and neurodegenerative diseases. Thus, SIRT3 activators represent a valuable therapeutic strategy for disorders such as Alzheimer's, Parkinson's, and metabolic syndromes, where

mitochondrial dysfunction is a defining pathological hallmark.[172]

PGC-1α modulators

Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) is a master regulator of mitochondrial biogenesis, oxidative metabolism, and cellular energy balance, making it a key target in therapies for neurodegenerative and metabolic diseases. As a transcriptional co-activator, PGC-1α partners with NRF1/2 and ERRα to drive genes required for mitochondrial DNA replication, respiratory chain assembly, and antioxidant defense.[173]High-throughput screening approaches are increasingly identifying small molecules that enhance PGC-1α activity, either directly or via upstream regulators such as AMPK (phosphorylation) and SIRT1 (deacetylation). Activation of PGC-1α stimulates mitochondrial proliferation, improves oxidative phosphorylation, enhances fatty acid oxidation, and up-regulates antioxidant enzymes including SOD and GPx.In disorders marked by mitochondrial dysfunction-such as Parkinson's, Huntington's, and ALS-pharmacological activation of PGC-1α has been shown to restore energy metabolism and improve neuronal survival. Thus, PGC-1α modulators identified through screening represent both valuable research tools and promising therapeutic candidates for reversing mitochondrial impairment at the transcriptional level.[174]

5.2 Targeted Drug Delivery Approaches

Mitochondria-penetrating peptides (MPPs)

Mitochondria-penetrating peptides (MPPs) are an advanced drug delivery platform engineered to transport therapeutic molecules across the selective mitochondrial membranes. The strong negative potential of the inner mitochondrial membrane (~ -150 to-180 mV) restricts entry of most drugs, particularly large or polar compounds. MPPs overcome this barrier through their amphipathic design, typically consisting of alternating cationic residues (arginine, lysine) and hydrophobic residues (phenylalanine, cyclohexylalanine), which enable both membrane interaction and electrophoretic uptake driven by the mitochondrial membrane potential.[175]By conjugating with diverse cargos-including antioxidants, enzyme inhibitors, and nucleic acids-MPPs achieve selective mitochondrial delivery without loss of targeting efficiency. Once inside the matrix, the therapeutic payload is released, enabling precise modulation of redox balance, mitochondrial dynamics, or permeability transition pore activity. This site-specific targeting enhances efficacy and reduces systemic toxicity, offering particular promise in neurodegenerative and mitochondrial disorders, where localized mitochondrial dysfunction is central to pathology.Thus, MPPs provide a versatile platform that links systemic drug administration to organelle-specific action, positioning them as a next-generation strategy in mitochondrial therapeutics.[176]

Liposomal and nanoparticle carriers with mitochondrial targeting ligands

Liposomal and nanoparticle-based delivery systems functionalized with mitochondrial-targeting ligands represent an advanced approach in mitochondrial therapeutics. These carriers encapsulate drugs, nucleic acids, peptides, or antioxidants within lipid vesicles or polymeric nanoparticles, protecting them from degradation and improving bioavailability. Mitochondrial specificity is achieved by surface modification with lipophilic cations (e.g., triphenylphosphonium, TPP^+) or mitochondria-homing peptides, which exploit the inner membrane potential ($\Delta\Psi m$) to drive selective accumulation within the organelle.Upon mitochondrial entry, the carriers release their therapeutic payload into the matrix, enabling targeted modulation of processes such as electron transport, ROS detoxification, or mitochondrial dynamics.[177] This localized delivery enhances efficacy, minimizes systemic toxicity, and provides superior control over drug action compared to conventional approaches. High-throughput screening further optimizes carrier parameters-lipid composition, size, charge, and surface chemistry-for maximal mitochondrial uptake.By merging nanotechnology with mitochondrial biology, these ligand-functionalized nanocarriers offer a powerful platform for next-generation treatments of mitochondrial and neurodegenerative diseases.[178]

Light-activated (photo pharmacological) mitochondrial drugs

Light-activated or photo-pharmacological mitochondrial drugs represent a next-generation strategy for precise subcellular therapy, enabling spatial and temporal control over drug activation. These agents are designed as photo responsive prodrugs, incorporating photolabile groups or photo chromic switches that release active compounds upon illumination with specific wavelengths. For mitochondrial targeting, they are frequently conjugated with lipophilic cations (e.g., triphenylphosphonium, TPP^+) or other ligands that exploit the organelle's negative membrane potential to promote selective accumulation.[179]Once localized within mitochondria, light exposure triggers bond cleavage or structural rearrangement, releasing the therapeutic payload directly into the matrix. This approach not only reduces systemic toxicity but also permits controlled modulation of mitochondrial function. Depending on design, photoactivation can either liberate antioxidants, regulate fission-fusion machinery, or generate reactive oxygen species (ROS) to trigger apoptosis in damaged or cancerous cells.By combining mitochondrial targeting with optical precision, photopharmacological drugs offer unprecedented control over therapeutic action, with significant potential for treating neurodegenerative and mitochondrial diseases where localized dysfunction is a central pathogenic feature.[180]

6. Clinical Trials and Translational Barriers

Table 2: Summary of mitochondrial-targeting agents in clinical pipelines

Agent	Mechanism of Action	Indication	Trial Phase	Clinical Trial Identifier (NCT No.)
Elamipretide (MTP-131)	Stabilizes cardiolipin in the inner mitochondrial membrane, reducing reactive oxygen species (ROS) production	Primary mitochondrial myopathy (PMM)	Phase II–III	NCT03323749
KH176 (Sonlicromanol)	Antioxidant and ROS-redox modulator, suppresses microsomal prostaglandin E synthase-1 (mPGES-1)	Mitochondrial diseases (e.g., MELAS, LHON)	Phase II–III	NCT02544217
Cysteamine Bitartrate (RP103)	Enhances glutathione biosynthesis, reducing oxidative stress	Leigh syndrome, MELAS, LHON	Phase II–III	NCT02023866
Devimistat (CPI-613)	Inhibits enzymes in the tricarboxylic acid (TCA) cycle, disrupting cancer cell metabolism	Pancreatic cancer, acute myeloid leukemia (AML)	Phase III	NCT04029688
Idebenone	Synthetic analog of coenzyme Q10, antioxidant properties	Leber's hereditary optic neuropathy (LHON)	Phase II–III	NCT00747487

Table 3: List of all category drug-Ongoing and completed clinical trial with trial no. and patents

S.no.	Category / Agent	Selected clinical trial(s) (NCT# - status / indication)	Representative patent(s) (patent no. - assignee)	Notes / key references
1	**Elamipretide (SS-31, MTP-131)**- mitochondria-targeting tetrapeptide that binds cardiolipin	**NCT03891875**ReCLAIM-2 - Phase II (dry AMD; randomized). **NCT06373731**ReNEW- Phase III program (dry AMD) - active/ongoing programs reported.	**US 11,261,213 B2** (crystalline salts of elamipretide) and other US patents (e.g., US 11,083,771/11,083,772 covering uses) - Stealth BioTherapeutics.	Elamipretide has been evaluated across mitochondrial myopathies, Barth syndrome and ophthalmic indications; Stealth holds multiple composition and use patents.
2	**MitoQ (mitoquinone/mitoquinol mesylate)**- TPP-conjugated antioxidant that accumulates in mitochondria	**NCT04851288** (oral MitoQ 20 mg/d - randomized placebo-controlled - recent cardiovascular/biomarker trials). Other early-phase neuro/vascular trials (multiple entries). Also newer trials listed (e.g., NCT06191965).	Representative patents on mitoquinone derivatives: **US 7,888,334 B2** and **US 2008/0161267 A1** covering mitoquinone derivatives and TPP-linked antioxidants - (assignees / inventors per patent record).	Widely studied mitochondrial antioxidant with numerous investigator-led and industry trials; MitoQ developer maintains patent family on TPP-linked antioxidants and formulations.
3	**Vatiquinone / EPI-743 (vatiquinone, PTC-743 / EPI-743)**- quinone antioxidant (α-tocotrienol quinone analogue)	**NCT01370447** (EPI-743 in mitochondrial respiratory chain diseases - completed/early studies). Several program trials (Friedreich ataxia, mitochondrial epilepsy, MDAS, MOVE-FA program) - mixed results in later trials (company press releases).	Patent families and composition/use filings published by Edison / PTC/assignees (see company disclosures and trial documentation). Representative summaries available on clinical development pages.	EPI-743/vatiquinone has advanced through multiple small/medium clinical programs (FA, Leigh, mitochondrial epilepsy); clinical readouts have been mixed and program status has evolved.
4	**Idebenone (Raxone®)**- short-	**NCT02774005** LEROS (Phase IV / open-label	Multiple composition and therapeutic use	Idebenone (marketed as Raxone in some regions) is

	chain benzoquinone (CoQ analog) used in LHON and other indications	study for LHON). **NCT02771379** post-authorisation safety / trial records; earlier randomized trials (e.g., Klopstock et al., 2011) showed clinical investigations in LHON.	patents / regulatory exclusivities held historically by companies (e.g., Santhera/others) - patent & regulatory families vary by jurisdiction (see DrugBank and company pages).	one of the better-documented mitochondrial therapeutics with completed clinical trials in Leber's hereditary optic neuropathy.
5	**TPP-conjugated small molecules & TPP delivery platform (e.g., Mito-TEMPO, other TPP-linkers)**- platform approach to drive accumulation	Representative clinical trials are fewer (many preclinical); a small number of TPP-conjugates have entered early-phase development. Specific trial IDs vary by compound - see ClinicalTrials.gov for "triphenylphosphonium" search results (multiple investigator studies).	Patents on TPP-conjugation chemistries and specific derivative families (for example, patents covering mitoquinone family and other TPP-linked antioxidants). Representative patents: US 2008/0161267 A1; US 7,888,334 B2.	Many TPP-conjugates remain at preclinical / early clinical stages; patent coverage focuses on the conjugation chemistry and composition of matter.
6	**Mitochondria-penetrating peptides (MPPs) & Szeto-Schiller (SS) peptides (e.g., SS-31 class / elamipretide overlaps here)**	Clinical development largely represented by elamipretide (SS-31) trials listed above; other MPPs are in preclinical/early clinical stages. See SS-peptide literature and company pipelines.	Patents covering MPP sequences, salts, formulations and therapeutic uses (e.g., WO/US family patents for SS peptides, peptide crystalline forms) - Stealth and collaborators hold key filings.	MPPs are an active patent space (composition/sequence/formulation/use); elamipretide is the clinical poster-child of this class.

Challenges:

Despite notable progress in the development of mitochondrial-targeted therapeutics, several challenges continue to impede their successful clinical translation. A key limitation is the blood–brain barrier (BBB), which restricts the entry of many candidate drugs into the central nervous system. Consequently, agents designed for neurodegenerative disorders often fail to achieve effective brain concentrations, necessitating innovative delivery strategies such as lipophilic modification, nanoparticle-based carriers, or receptor-mediated transport.Another major hurdle is the risk of off-target toxicity, as mitochondria are ubiquitous and indispensable for cellular homeostasis.[181] Modulators of mitochondrial dynamics, redox balance, or biogenesis may inadvertently disrupt healthy mitochondria, resulting in systemic side effects. Achieving precise organelle-specific targeting without collateral damage remains a critical challenge.In addition, patient heterogeneity complicates therapeutic outcomes. Variability in genetic background, mitochondrial mutations, disease stage, and bio-energetic capacity makes it difficult to establish uniform biomarkers of efficacy or predict patient responses. This highlights the importance of personalized medicine, including stratification based on mitochondrial genotypes, metabolic profiles, or responsiveness to NAD^+-boosting interventions.Collectively, these issues underscore the complexity of moving mitochondrial-targeted agents from bench to bedside and emphasize the need for smarter delivery systems, more selective molecular designs, and individualized treatment strategies to realize their full therapeutic potential.[182]

7. Future Directions

Table 3: CRISPR/Cas9 and mitoTALENs for correcting mitochondrial DNA mutations.[183,184]

Feature	CRISPR/Cas9 (Mitochondrial Adaptation)	MitoTALENs
Mechanism	RNA-guided nuclease system; uses guide RNA (gRNA) to direct Cas9 to specific mtDNA sites	Protein-based nucleases engineered from TALE proteins fused with FokI nuclease, targeting mutant mtDNA sequences
Delivery Challenge	Major hurdle: efficient import of gRNA and Cas9 into mitochondria remains unresolved	Protein-only system; easier mitochondrial import as mitoTALENs are engineered with mitochondrial targeting sequences (MTS)
Editing Strategy	Aimed at direct correction or cleavage of pathogenic mtDNA variants (still experimental)	Selective cleavage of mutant mtDNA → promotes replication of wild-type mtDNA (**heteroplasmy shifting**)
Precision	Potentially high, but risk of off-target cleavage due to incomplete mitochondrial import control	High sequence specificity, as recognition is based on modular TALE repeats
Current Status	Early preclinical stage; proof-of-concept studies ongoing	Demonstrated efficacy in cell and animal models for heteroplasmic mitochondrial disorders
Therapeutic Potential	Long-term: correction of diverse mtDNA mutations, broader applications if delivery solved	More immediately translatable for diseases driven by hetero plasmic mtDNA mutations
Limitations	Inefficient mitochondrial delivery of CRISPR components; risk of off-target edits	Limited to heteroplasmy shifting (cannot directly "fix" mutations); protein delivery challenges remain
Clinical Translation Outlook	Promising but distant-requires major breakthroughs in mitochondrial import systems	Closer to clinical use; strong candidate for hetero plasmic mtDNA disease therapy

7.2 Multi-target drug strategies (e.g., polypharmacology)

Mitochondrial dysfunction in neurodegenerative and metabolic disorders is inherently multifactorial, arising from a convergence of defects across several interconnected pathways. This complexity limits the effectiveness of conventional single-target therapeutic strategies and underscores the need for multi-target drug approaches, or polypharmacology. Unlike traditional agents that act on a single protein or signaling cascade, polypharmacological compounds are designed to simultaneously influence diverse aspects of mitochondrial function, including bioenergetics, redox balance, calcium homeostasis, and quality-control processes such as mitophagy.[185]By engaging multiple mechanisms in parallel, such agents have the potential to produce synergistic effects, thereby enhancing mitochondrial resilience and more effectively restoring cellular equilibrium compared to single-target interventions. Mechanistically, these compounds may integrate antioxidant properties with modulators of mitochondrial dynamics or NAD^+-boosting activity, linking protective actions with repair and recovery processes. Furthermore, multi-target strategies may overcome the compensatory feedback mechanisms that frequently compromise the efficacy of single-pathway drugs.Looking ahead advances in high-throughput screening and computational modeling will be critical for the identification and optimization of multifunctional molecules with tailored therapeutic profiles. Collectively, polypharmacology represents a promising paradigm to address the inherent complexity of mitochondrial disorders, offering the potential for more comprehensive, durable, and patient-specific clinical benefits.[186]

7.3 Organoid and iPSC-derived neuronal models to test mitochondrial drugs

Organoid and induced pluripotent stem cell (iPSC)-derived neuronal models have transformed the study of mitochondrial dysfunction in neurodegenerative diseases by more accurately recapitulating human neuronal physiology and three-dimensional brain architecture than traditional systems. iPSC-derived neurons provide patient-specific platforms that capture authentic mitochondrial genotypes and disease mutations, while brain organoids incorporate complex features such as neuron–glia communication and vascular-like structures, enabling the study of bioenergetics, dynamics, and neuroinflammation in a biologically relevant context. These models not only allow rigorous evaluation of mitochondrial-targeted therapeutics for efficacy, toxicity, and rescue potential but also support high-throughput screening and mechanistic studies, thereby accelerating translation into clinical applications. By overcoming species-specific limitations and reflecting patient heterogeneity, iPSC and organoid technologies represent indispensable tools for advancing precision medicine and enhancing the

likelihood of success in mitochondrial drug development.[187]

7.4 AI-driven drug discovery focused on mitochondrial proteome

The integration of artificial intelligence (AI) and machine learning into drug discovery offers a transformative approach to targeting mitochondrial dysfunction by enabling comprehensive analysis of the mitochondrial proteome. Owing to its complexity—spanning oxidative phosphorylation, metabolite transport, apoptosis regulation, and quality control—traditional methods often fall short in identifying optimal targets or predicting off-target effects. AI-driven platforms can integrate multi-omics datasets to reveal novel protein interactions, post-translational modifications, and dysregulated networks, while deep learning algorithms accelerate target prioritization, molecular docking, and compound optimization with high precision. Beyond single targets, AI also supports polypharmacology by predicting how multi-target agents interact with the mitochondrial proteome to restore cellular balance, and can further incorporate patient-specific data to advance personalized therapeutics. By streamlining early drug discovery, lowering costs, and enhancing predictions of efficacy and safety, AI-guided strategies hold significant potential to accelerate the development of precision medicines for mitochondrial diseases.[188]

Table 4: Comparative Overview of Models and Approaches in Mitochondrial Drug Discovery.[189-91]

Approach	Key Features	Advantages	Limitations	Relevance to Mitochondrial Drug Discovery
Traditional Models (cell lines & animals)	Immortalized cell lines; rodent models	Well-established, cost-effective, reproducible; in vivo systemic effects assessed	Limited human relevance; species differences; poor replication of complex brain physiology	Useful for initial screening and systemic toxicity evaluation
iPSC-Derived Neurons	Patient-specific neurons from reprogrammed cells	Capture authentic genetic background (including mtDNA mutations); scalable; personalized disease modeling	Labor-intensive; variable differentiation efficiency; immature phenotypes	Enables study of patient-specific mitochondrial dysfunction, bioenergetics, and therapeutic responses
Brain Organoids	3D multicellular neural tissue structures	Mimic tissue architecture; include neuron-glia interactions and vascular-like features; recapitulate network-level dysfunctions	High variability; incomplete maturation; lack of full vascularization	Valuable for modeling neuroinflammation, mitochondrial dynamics, and drug effects at network level
AI-Driven Drug Discovery (Mitochondrial Proteome Focus)	Computational modeling, machine learning on mitochondrial protein networks	High-throughput in silico screening; predicts polypharmacology targets; integrates omics data; reduces cost & time	Requires high-quality datasets; interpretability challenges; needs validation in biological systems	Identifies novel mitochondrial targets, optimizes multi-target agents, accelerates candidate selection

8. Conclusion

Mitochondria are now recognized as pivotal regulators in neurodegenerative disorders, serving not only as cellular powerhouses but also as critical determinants of neuronal viability. Beyond ATP generation, they govern calcium buffering, reactive oxygen species (ROS) production, mitochondrial dynamics, and quality-control pathways, processes that are intimately linked to disease mechanisms. Perturbation of these functions precipitates bio-energetic collapse, oxidative damage, defective mitophagy, and impaired calcium homeostasis, ultimately compromising synaptic integrity and neuronal survival.Importantly, mitochondria act as hubs where genetic, metabolic, and environmental stressors converge, amplifying cellular injury and driving the progression of neurodegeneration. This central role underscores the urgency of therapeutic strategies directed at restoring mitochondrial function and resilience. Advances in mitochondrial biology continue to reveal novel molecular targets and intervention strategies, placing mitochondria at the forefront of neurodegenerative research. Restoring mitochondrial health therefore holds significant potential not only to slow or reverse disease trajectories but also to improve patient quality of life and longevity.

List of Abbreviations

ABAD- Aβ Binding Alcohol Dehydrogenase

AD- Alzheimer's disease

AMPK- AMP-Activated Protein Kinase

ALS - Amyotrophic Lateral Sclerosis

ATP- Adenosine Triphosphate

BBB- Blood–Brain Barrier

Ca^{2+} - Calcium Ion

CoQ10 - Coenzyme Q10

CRISPR - Clustered Regularly Interspaced Short Palindromic Repeats

DCA - Dichloroacetate

Drp1 - Dynamin-Related Protein 1

ETC - Electron Transport Chain

FUS - Fused in Sarcoma Protein

HD -Huntington's disease

LC3 - Microtubule-Associated Proteins 1A/1B Light Chain 3

MAMs - Mitochondria-Associated Membranes

MCU - Mitochondrial Calcium Uniporter

MFN1/2 - Mitofusin 1 and 2

mPTP - Mitochondrial Permeability Transition Pore

mtDNA - Mitochondrial DNA

Mdivi-1 - Mitochondrial Division Inhibitor 1

MPP - Mitochondria-Penetrating Peptides

MPTP - 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NAD^+ - Nicotinamide Adenine Dinucleotide (oxidized form)

NMN - Nicotinamide Mononucleotide

NR - Nicotinamide Riboside

OPA1 - Optic Atrophy Protein 1

OXPHOS - Oxidative Phosphorylation

PARP - Poly (ADP-Ribose) Polymerase

PD -Parkinson's disease

PGC-1α - Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha

PI3K - Phosphoinositide 3-Kinase

PINK1 - PTEN-Induced Kinase 1

ROS - Reactive Oxygen Species

RyR- Ryanodine Receptor

SIRT1/3 - Sirtuin 1 and 3

SOD1 - Superoxide Dismutase 1

TDP-43 - TAR DNA-binding Protein 43

TIM/TOM - Translocase of Inner/Outer Mitochondrial Membrane

ULK1 - Unc-51 Like Autophagy Activating Kinase 1

Acknowledgements

The authors are thankful to Principal and Management of the Columbia Institute of Pharmacy (C.G.) and Pt J.N.M. Medical College, Railway Station Rd, Moudhapara, Raipur for providing the necessary facilities to complete this manuscript.

Ethics approval and consent to participate: This manuscript is a review. Hence, no experiments in animals or humans are included in this study, so ethical approval and consent are not required.

Clinical Trial No: The manuscript is a review article (not a part of Clinical trial), hence no Clinical trial no is applicable.

Consent for publication: This manuscript does not contain any personal data. Hence, no consent is required.

Availability of data and material: Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Conflict of interest: The authors declare no conflicts of interest.

Funding: The authors received no funding from private /Govt./other organizations to complete this manuscript.

References:

1. Kathiresan DS, Balasubramani R, Marudhachalam K, Jaiswal P, Ramesh N, Sureshbabu SG, Puthamohan VM, Vijayan M. Role of mitochondrial dysfunctions in neurodegenerative disorders: advances in mitochondrial biology. Molecular Neurobiology. 2025 Jun;62(6):6827-55.https://doi.org/10.1007/s12035-024-04469-x
2. Cardanho-Ramos C, Morais VA. Mitochondrial biogenesis in neurons: how and where. International journal of molecular sciences. 2021 Dec 2;22(23):13059.https://doi.org/10.3390/ijms222313059
3. Fedorova A, Jovisic N, Vallverdù J, Battistoni S, Jovicic M, Medojević M, Toschev A, Alshanskaia E, Talanov M, Erokhin V. Advancing Neural Networks: Innovations and Impacts on Energy Consumption. Advanced Electronic Materials. 2024 Dec;10(12):2400258. https://doi.org/10.1002/aelm.202400258
4. Bereiter-Hahn J, Jendrach M. Environmental Stress: Mitochondria as Targets and Stressors in Cellular Metabolism. InStress Challenges and Immunity in Space: From Mechanisms to Monitoring and Preventive Strategies 2019 Nov 28 (pp. 43-70). Cham: Springer International Publishing.https://doi.org/10.1007/978-3-030-16996-1_5
5. Ciurea AV, Mohan AG, Covache-Busuioc RA, Costin HP, Glavan LA, Corlatescu AD, Saceleanu VM. Unraveling molecular and genetic insights into neurodegenerative diseases: advances in understanding Alzheimer's, Parkinson's, and Huntington's diseases and amyotrophic lateral sclerosis. International journal of molecular sciences. 2023 Jun 28;24(13):10809.https://doi.org/10.3390/ijms241310809
6. Wu Y, Chen M, Jiang J. Mitochondrial dysfunction in neurodegenerative diseases and drug targets via apoptotic signaling. Mitochondrion. 2019 Nov 1;49:35-45.https://doi.org/10.1016/j.mito.2019.07.003
7. Zong Y, Li H, Liao P, Chen L, Pan Y, Zheng Y, Zhang C, Liu D, Zheng M, Gao J. Mitochondrial dysfunction: mechanisms and advances in

therapy. Signal transduction and targeted therapy. 2024 May 15;9(1):124.https://doi.org/10.1038/s41392-024-01839-8

8. Shi Z, Wang XM, Duan WW, Du YL, Ling SK, Zhang Z, Wang GD, Zhao D, Ding JJ, Zhang K, Li A. Neuroplasticity and brain health: insights from natural torpor. Biological Reviews. 2025.https://doi.org/10.1111/brv.70069

9. Feofilaktova T, Kushnireva L, Segal M, Korkotian E. Calcium signaling in postsynaptic mitochondria: mechanisms, dynamics, and role in ATP production. Frontiers in Molecular Neuroscience. 2025 Jul 21;18:1621070.https://doi.org/10.3389/fnmol.2025.1621070

10. Feofilaktova T, Kushnireva L, Segal M, Korkotian E. Calcium signaling in postsynaptic mitochondria: mechanisms, dynamics, and role in ATP production. Frontiers in Molecular Neuroscience. 2025 Jul 21;18:1621070. https://doi.org/10.3389/fnmol.2025.1621070

11. Chintaluri C, Vogels TP. Metabolically regulated spiking could serve neuronal energy homeostasis and protect from reactive oxygen species. Proceedings of the National Academy of Sciences. 2023 Nov 28;120(48):e2306525120.https://doi.org/10.1073/pnas.2306525120

12. Gulino R. Synaptic dysfunction and plasticity in amyotrophic lateral sclerosis. International Journal of Molecular Sciences. 2023 Feb 27;24(5):4613.https://doi.org/10.3390/ijms24054613

13. Gao T, Hu Y, Zhang H, Shi R, Song Y, Ding M, Gao F. Aerobic Capacity Beyond Cardiorespiratory Fitness Linking Mitochondrial Function, Disease Resilience and Healthy Aging. The FASEB Journal. 2025 Jun 15;39(11):e70655. https://doi.org/10.1096/fj.202500554R

14. Plascencia-Villa G, Perry G. Exploring molecular targets for mitochondrial therapies in neurodegenerative diseases. International Journal of Molecular Sciences. 2023 Aug 6;24(15):12486. https://doi.org/10.3390/ijms241512486

15. Şerban M, Toader C, Covache-Busuioc RA. The Redox Revolution in Brain Medicine: Targeting Oxidative Stress with AI, Multi-Omics and Mitochondrial Therapies for the Precision Eradication of Neurodegeneration. International Journal of Molecular Sciences. 2025 Aug 3;26(15):7498.https://doi.org/10.3390/ijms26157498

16. Li Y, Li XM, Wei LS, Ye JF. Advancements in mitochondrial-targeted nanotherapeutics: overcoming biological obstacles and optimizing drug delivery. Frontiers in Immunology. 2024 Oct 17;15:1451989.https://doi.org/10.3389/fimmu.2024.1451989

17. Hu N, Chen Z, Zhao X, Peng X, Wu Y, Yang K, Sun T. Endothelial dysfunction in Huntington's disease: pathophysiology and therapeutic implications. International Journal of Molecular Sciences. 2025 Feb 8;26(4):1432.https://doi.org/10.3390/ijms26041432

18. Batis N, Brooks JM, Payne K, Sharma N, Nankivell P, Mehanna H. Lack of predictive tools for conventional and targeted cancer therapy: Barriers to biomarker development and clinical translation. Advanced Drug Delivery Reviews. 2021 Sep 1;176:113854.https://doi.org/10.1016/j.addr.2021.113854

19. Cunha-Oliveira T, Montezinho L, Simões RF, Carvalho M, Ferreiro E, Silva FS. Mitochondria: a promising convergent target for the treatment of amyotrophic lateral sclerosis. Cells. 2024 Jan 29;13(3):248.https://doi.org/10.3390/cells13030248

20. Liang Y, Rubinstein JL. Structural analysis of mycobacterial electron transport chain complexes by cryoEM. Biochemical Society Transactions. 2023 Feb 27;51(1):183-93.https://doi.org/10.1042/BST20220611

21. Peng S, Gao J, Stojkov D, Yousefi S, Simon HU. Established and emerging roles for mitochondria in neutrophils. Immunological Reviews. 2023 Mar;314(1):413-26. https://doi.org/10.1111/imr.13158

22. Padavannil A, Ayala-Hernandez MG, Castellanos-Silva EA, Letts JA. The mysterious multitude: structural perspective on the accessory subunits of respiratory complex I. Frontiers in molecular biosciences. 2022 Jan 3;8:798353.https://doi.org/10.3389/fmolb.2021.798353

23. Priya HK, Jha KP, Kumar N, Singh S. Reactive Oxygen Species and Mitochondrial Calcium's Roles in the Development of Atherosclerosis. Current Pharmaceutical Design.2024 Jun 1;30(23):1812-21. https://doi.org/10.2174/0113816128303026240514111200

24. Eaton AF, Merkulova M, Brown D. The H+-ATPase (V-ATPase): from proton pump to signaling complex in health and disease. American Journal of Physiology-Cell Physiology. 2021 Mar 1;320(3):C392-414.https://doi.org/10.1152/ajpcell.00442.2020

25. Benit P, Goncalves J, El Khoury R, Rak M, Favier J, Gimenez-Roqueplo AP, Rustin P. Succinate dehydrogenase, succinate, and superoxides: a genetic, epigenetic, metabolic, environmental explosive crossroad. Biomedicines. 2022 Jul 25;10(8):1788.https://doi.org/10.3390/biomedicines10081788

26. Muras V, Toulouse C, Fritz G, Steuber J. Respiratory membrane protein complexes convert chemical energy. Bacterial Cell Walls and Membranes. 2019 Jun 19:301-35.https://doi.org/10.1007/978-3-030-18768-2_10

27. Mantle D, Dewsbury M, Hargreaves IP. The Ubiquinone-Ubiquinol redox cycle and Its clinical consequences: An overview. International Journal of Molecular Sciences. 2024 Jun 20;25(12):6765.https://doi.org/10.3390/ijms25126765

28. Zhou H, Wang K, He L, Liu Z, Kong D, Zhang Q, Jin S, Han Y, Guan Q, Sheng G. Periplasmic transport channels to accelerate the proton motive force for efficient groundwater bioelectrocatalytic Cr (VI) reduction. Water Research. 2025 Sep 9:124581.https://doi.org/10.1016/j.watres.2025.124581

29. Heine KB, Parry HA, Hood WR. How does density of the inner mitochondrial membrane influence mitochondrial performance?. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. 2023 Feb 1;324(2):R242-8.https://doi.org/10.1152/ajpregu.00254.2022

30. Hauser D, Sode M, Andreeva EA, Parey K, Barends TR. Rieske Iron-Sulfur Cluster Proteins from an Anaerobic Ammonium Oxidizer Suggest Unusual Energetics in their Parent Rieske/cytochrome b complexes. bioRxiv. 2025 Jun 27:2025-06.https://doi.org/10.1101/2025.06.25.661457

31. Paduvari R, Arekal R, Somashekara DM. Uncovering the mysteries of bacterial cytochrome c oxidases: A review on structural and molecular insights for potential application. International Journal of Biological Macromolecules. 2025 May 1;309:142773.https://doi.org/10.1016/j.ijbiomac.2025.142773

32. Protasoni M, Zeviani M. Mitochondrial structure and bioenergetics in normal and disease conditions. International journal of molecular sciences. 2021 Jan 8;22(2):586. https://doi.org/10.3390/ijms22020586

33. Kostova I. The role of complexes of biogenic metals in living organisms. Inorganics. 2023 Jan 25;11(2):56. https://doi.org/10.3390/inorganics11020056

34. Zharova TV, Grivennikova VG, Borisov VB. F1· Fo ATP Synthase/ATPase: contemporary view on unidirectional catalysis. International Journal of Molecular Sciences. 2023 Mar 12;24(6):5417.5417; https://doi.org/10.3390/ijms24065417

35. Zharova TV, Grivennikova VG, Borisov VB. F1· Fo ATP Synthase/ATPase: contemporary view on unidirectional catalysis. International Journal of Molecular Sciences. 2023 Mar 12;24(6):5417. https://doi.org/10.3390/ijms24065417

36. Schirrmacher V. Mitochondria at work: new insights into regulation and dysregulation of cellular energy supply and metabolism. Biomedicines. 2020 Nov 22;8(11):526. https://doi.org/10.3390/biomedicines8110526

37. Venditti P, Di Meo S. The role of reactive oxygen species in the life cycle of the mitochondrion. International journal of molecular sciences. 2020 Mar 21;21(6):2173.https://doi.org/10.3390/ijms21062173

38. Du H, Xu T, Yu S, Wu S, Zhang J. Mitochondrial metabolism and cancer therapeutic innovation. Signal Transduction and Targeted Therapy. 2025 Aug 4;10(1):245.https://doi.org/10.1038/s41392-025-02311-x

39. Ragni M, Ruocco C, Nisoli E. Mitochondrial uncoupling, energy substrate utilization, and brown adipose tissue as therapeutic targets in cancer. npj Metabolic Health and Disease. 2025 Sep 22;3(1):37.https://doi.org/10.1038/s44324-025-00080-3

40. Sayehmiri F, Motamedi F, Batool Z, Naderi N, Shaerzadeh F, Zoghi A, Rezaei O, Khodagholi F, Pourbadie HG. Mitochondrial plasticity and synaptic plasticity crosstalk; in health and Alzheimer's disease. CNS neuroscience & therapeutics. 2024 Aug;30(8):e14897. https://doi.org/10.1111/cns.14897

41. Cenini G, Lloret A, Cascella R. Oxidative stress in neurodegenerative diseases: from a mitochondrial point of view. Oxidative medicine and cellular longevity. 2019;2019(1):2105607. https://doi.org/10.1155/2019/2105607

42. Mahapatra C, Kishore A, Gawad J, Al-Emam A, Kouzeiha RA, Rusho MA. Review of electrophysiological models to study membrane potential changes in breast cancer cell transformation and tumor progression. Frontiers in Physiology. 2025 Mar 5;16:1536165. https://doi.org/10.3389/fphys.2025.1536165

43. Llavanera M, Delgado-Bermúdez A, Olives S, Mateo-Otero Y, Recuero S, Bonet S, Fernández-Fuertes B, Yeste M, Barranco I. Glutathione S-transferases play a crucial role in mitochondrial function, plasma membrane stability and oxidative regulation of mammalian sperm. Antioxidants. 2020 Jan 24;9(2):100. https://doi.org/10.3390/antiox9020100

44. Morciano G, Naumova N, Koprowski P, Valente S, Sardão VA, Potes Y, Rimessi A, Wieckowski MR, Oliveira PJ. The mitochondrial permeability transition pore: an evolving concept critical for cell life and death. Biological Reviews. 2021 Dec;96(6):2489-521. https://doi.org/10.1111/brv.12764

45. Tassone A, Meringolo M, Ponterio G, Bonsi P, Schirinzi T, Martella G. Mitochondrial bioenergy in neurodegenerative disease: Huntington and Parkinson. International Journal of Molecular Sciences. 2023 Apr 13;24(8):7221.https://doi.org/10.3390/ijms24087221

46. Seager R, Lee L, Henley JM, Wilkinson KA. Mechanisms and roles of mitochondrial localisation and dynamics in neuronal function. Neuronal Signaling. 2020 Jun;4(2):NS20200008.https://doi.org/10.1042/NS20200008

47. Wang N, Wang X, Lan B, Gao Y, Cai Y. DRP1, fission and apoptosis. Cell Death Discovery. 2025 Apr 7;11(1):150.https://doi.org/10.1038/s41420-025-02458-0

48. Adebayo M, Singh S, Singh AP, Dasgupta S. Mitochondrial fusion and fission: the fine-tune balance for cellular homeostasis. The FASEB Journal. 2021 Jun;35(6):e21620. https://doi.org/10.1096/fj.202100067R

49. Kawano I, Bazila B, Ježek P, Dlasková A. Mitochondrial dynamics and cristae shape changes during metabolic reprogramming. Antioxidants & Redox Signaling. 2023 Oct 1;39(10-12):684-707.https://doi.org/10.1089/ars.2023.0268

50. Quiles JM, Gustafsson ÅB. The role of mitochondrial fission in cardiovascular health and disease. Nature Reviews Cardiology. 2022 Nov;19(11):723-36.https://doi.org/10.1038/s41569-022-00703-y

51. Theocharopoulou G. The ubiquitous role of mitochondria in Parkinson and other neurodegenerative diseases. AIMS neuroscience. 2020 Mar 25;7(1):43. 10.3934/Neuroscience.2020004

52. Iorio R, Celenza G, Petricca S. Mitophagy: molecular mechanisms, new concepts on parkin activation and the emerging role of AMPK/ULK1 axis. Cells. 2021 Dec 23;11(1):30.https://doi.org/10.3390/cells11010030

53. Vargas JN, Hamasaki M, Kawabata T, Youle RJ, Yoshimori T. The mechanisms and roles of selective autophagy in mammals. Nature reviews Molecular cell biology. 2023 Mar;24(3):167-85.https://doi.org/10.1038/s41580-022-00542-2

54. Vizziello M, Borellini L, Franco G, Ardolino G. Disruption of mitochondrial homeostasis: The role of PINK1 in Parkinson's disease. Cells. 2021 Nov 4;10(11):3022. https://doi.org/10.3390/cells10113022

55. Mandal A, Drerup CM. Axonal transport and mitochondrial function in neurons. Frontiers in Cellular Neuroscience. 2019 Aug 9;13:373.https://doi.org/10.3389/fncel.2019.00373

56. Alberti P, Semperboni S, Cavaletti G, Scuteri A. Neurons: the interplay between cytoskeleton, ion channels/transporters and mitochondria. Cells. 2022 Aug 11;11(16):2499.https://doi.org/10.3390/cells11162499

57. Fenton AR, Jongens TA, Holzbaur EL. Mitochondrial dynamics: Shaping and remodeling an organelle network. Current opinion in cell biology. 2021 Feb 1;68:28-36.https://doi.org/10.1016/j.ceb.2020.08.014

58. Scott DN, Frank MJ. Adaptive control of synaptic plasticity integrates micro-and macroscopic network function. Neuropsychopharmacology. 2023 Jan;48(1):121-44.https://doi.org/10.1038/s41386-022-01374-6

59. Atkinson CS, Cheng-Boivin Z, Larochelle N, Minotti S, Gentil BJ. CK1α, FAM83H, and FAM83B contribute to bundling of neurofilaments and are sequestered in cellular and mice models of ARSACS. bioRxiv. 2024 Oct 1:2024-10.https://doi.org/10.1101/2024.10.01.616079

60. Chinopoulos C, Adam-Vizi V. Calcium, mitochondria and oxidative stress in neuronal pathology: novel aspects of an enduring theme. The FEBS journal. 2006 Feb;273(3):433-50. https://doi.org/10.1111/j.1742-4658.2005.05103

61. Marchi S, Pinton P. The mitochondrial calcium uniporter complex: molecular components, structure and physiopathological implications. The Journal of physiology. 2014 Mar 1;592(5):829-39.https://doi.org/10.1113/jphysiol.2013.268235

62. Mammucari C, Raffaello A, Reane DV, Rizzuto R. Molecular structure and pathophysiological roles of the mitochondrial calcium uniporter. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2016 Oct 1;1863(10):2457-64.https://doi.org/10.1016/j.bbamcr.2016.03.006

63. Garbincius JF, Elrod JW. Mitochondrial calcium exchange in physiology and disease. Physiological reviews. 2022 Apr 1;102(2):893-992.https://doi.org/10.1152/physrev.00041.2020

64. Borkum JM. The tricarboxylic acid cycle as a central regulator of the rate of aging: implications for metabolic interventions. Advanced Biology. 2023 Jul;7(7):2300095. https://doi.org/10.1002/adbi.202300095

65. Penna C, Perrelli MG, Pagliaro P. Mitochondrial pathways, permeability transition pore, and redox signaling in cardioprotection: therapeutic implications. Antioxidants & redox signaling. 2013 Feb 10;18(5):556-99.https://doi.org/10.1089/ars.2011.4459

66. Feno S, Butera G, Vecellio Reane D, Rizzuto R, Raffaello A. Crosstalk between calcium and ROS in pathophysiological conditions. Oxidative medicine and cellular longevity. 2019;2019(1):9324018.https://doi.org/10.1155/2019/9324018

67. Oyewole AO, Birch-Machin MA. Mitochondria-targeted antioxidants. The FASEB Journal. 2015 Dec;29(12):4766-71. https://doi.org/10.1096/fj.15-275404

68. Walters GC, Usachev YM. Mitochondrial calcium cycling in neuronal function and neurodegeneration. Frontiers in cell and developmental biology. 2023 Jan 24;11:1094356.https://doi.org/10.3389/fcell.2023.1094356

69. Szymański J, Janikiewicz J, Michalska B, Patalas-Krawczyk P, Perrone M, Ziółkowski W, Duszyński J, Pinton P, Dobrzyń A, Więckowski MR. Interaction of mitochondria with the endoplasmic reticulum and plasma membrane in calcium homeostasis, lipid trafficking and mitochondrial structure. International Journal of Molecular Sciences. 2017 Jul 20;18(7):1576. https://doi.org/10.3390/ijms18071576

70. Loncke J, Kerkhofs M, Kaasik A, Bezprozvanny I, Bultynck G. Recent advances in understanding IP3R function with focus on ER-mitochondrial Ca2+ transfers. Current Opinion in Physiology. 2020 Oct 1;17:80-8.https://doi.org/10.1016/j.cophys.2020.07.011

71. Wang Y, Zhang X, Wen Y, Li S, Lu X, Xu R, Li C. Endoplasmic reticulum-mitochondria contacts: a potential therapy target for

cardiovascular remodeling-associated diseases. Frontiers in Cell and Developmental Biology. 2021 Nov 10;9:774989.https://doi.org/10.3389/fcell.2021.774989

72. Area-Gomez E, de Groof A, Bonilla E, Montesinos J, Tanji K, Boldogh I, Pon L, Schon EA. A key role for MAM in mediating mitochondrial dysfunction in Alzheimer disease. Cell death & disease. 2018 Feb 28;9(3):335.https://doi.org/10.1038/s41419-017-0215-0

73. Tabassum N, Kheya IS, Asaduzzaman S, Maniha S, Fayz AH, Zakaria A, Noor R. A review on the possible leakage of electrons through the electron transport chain within mitochondria. Life Sci. 2020;6(1):105-13. https://doi.org/10.1111/j.1469-7793.2003.00335.

74. Wang Y, Zhang SX, Gozal D. Reactive oxygen species and the brain in sleep apnea. Respiratory physiology & neurobiology. 2010 Dec 31;174(3):307-16.https://doi.org/10.1016/j.resp.2010.09.001

75. Checa J, Aran JM. Reactive oxygen species: drivers of physiological and pathological processes. Journal of Inflammation research. 2020 Dec 2:1057-73.https://doi.org/10.2147/JIR.S275595

76. Jurcău MC, Andronie-Cioara FL, Jurcău A, Marcu F, Țiț DM, Pașcalău N, Nistor-Cseppentö DC. The link between oxidative stress, mitochondrial dysfunction and neuroinflammation in the pathophysiology of Alzheimer's disease: therapeutic implications and future perspectives. Antioxidants. 2022 Oct 31;11(11):2167.https://doi.org/10.3390/antiox11112167

77. Yan SD, Stern DM. Mitochondrial dysfunction and Alzheimer's disease: role of amyloid-β peptide alcohol dehydrogenase (ABAD). International journal of experimental pathology. 2005 Jun;86(3):161-71. https://doi.org/10.1111/j.0959-9673.2005.00427.

78. Takuma K, Yao J, Huang J, Xu H, Chen X, Luddy J, Trillat AC, Stern DM, Arancio O, Yan SS. ABAD enhances Aβ-induced cell stress via mitochondrial dysfunction. The FASEB Journal. 2005 Apr;19(6):1-25. https://doi.org/10.1096/fj.04-2582fje

79. R. Valaasani K, Sun Q, Hu G, Li J, Du F, Guo Y, A. Carlson E, Gan X, S. Yan S. Identification of human ABAD inhibitors for rescuing Aβ-mediated mitochondrial dysfunction. Current Alzheimer research. 2014 Feb 1;11(2):128-36.https://doi.org/10.2174/1567205011666140130150108

80. Swerdlow RH. The mitochondrial hypothesis: dysfunction, bioenergetic defects, and the metabolic link to Alzheimer's disease. International review of neurobiology. 2020 Jan 1;154:207-33.https://doi.org/10.1016/bs.irn.2020.01.008

81. Cheekatla SR. Benzothiazole-Based Therapeutics: FDA Insights and Clinical Advances. Chemistry. 2025 Jul 25;7(4):118. https://doi.org/10.3390/chemistry7040118

82. Pinho CM, Teixeira PF, Glaser E. Mitochondrial import and degradation of amyloid-β peptide. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 2014 Jul 1;1837(7):1069-74.https://doi.org/10.1016/j.bbabio.2014.02.007

83. Plácido AI, Pereira CM, Duarte AI, Candeias E, Correia SC, Santos RX, Carvalho C, Cardoso S, Oliveira CR, Moreira PI. The role of endoplasmic reticulum in amyloid precursor protein processing and trafficking: implications for Alzheimer's disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2014 Sep 1;1842(9):1444-53.https://doi.org/10.1016/j.bbadis.2014.05.003

84. Ottens F, Franz A, Hoppe T. Build-UPS and break-downs: metabolism impacts on proteostasis and aging. Cell Death & Differentiation. 2021 Feb;28(2):505-21.https://doi.org/10.1038/s41418-020-00682-y

85. Wang X, Zheng W. Ca2+ homeostasis dysregulation in Alzheimer's disease: a focus on plasma membrane and cell organelles. The FASEB Journal. 2019 Jun;33(6):6697-712. https://doi.org/10.1096/fj.201801751R

86. Briston T, Hicks AR. Mitochondrial dysfunction and neurodegenerative proteinopathies: mechanisms and prospects for therapeutic intervention. Biochemical Society Transactions. 2018 Aug 20;46(4):829-42.https://doi.org/10.1042/BST20180025

87. Sahu P, Satapathy T. Immunopharmacology of senescence: targeting the senescence-associated secretory phenotype (SASP)-a mechanism-based review. Inflammopharmacology. 2025 Jul 26:1-20. https://doi.org/10.1007/s10787-025-01867-y

88. Cario A, Berger CL. Tau, microtubule dynamics, and axonal transport: New paradigms for neurodegenerative disease. Bioessays. 2023 Aug;45(8):2200138. https://doi.org/10.1002/bies.202200138

89. Zaninello M, Bean C. Highly specialized mechanisms for mitochondrial transport in neurons: from intracellular mobility to intercellular transfer of mitochondria. Biomolecules. 2023 Jun 3;13(6):938. https://doi.org/10.3390/biom13060938

90. Reddy PH. Abnormal tau, mitochondrial dysfunction, impaired axonal transport of mitochondria, and synaptic deprivation in Alzheimer's disease. Brain research. 2011 Sep 30;1415:136-48.https://doi.org/10.1016/j.brainres.2011.07.052

91. Zündorf G, Reiser G. Calcium dysregulation and homeostasis of neural calcium in the molecular mechanisms of neurodegenerative diseases provide multiple targets for neuroprotection. Antioxidants & redox signaling. 2011 Apr 1;14(7):1275-88.https://doi.org/10.1089/ars.2010.3359

92. Chen H, Chan DC. Mitochondrial dynamics–fusion, fission, movement, and mitophagy–in neurodegenerative diseases. Human molecular genetics. 2009 Oct 15;18(R2):R169-76.https://doi.org/10.1093/hmg/ddp326

93. Wang S, Tan J, Miao Y, Zhang Q. Mitochondrial dynamics, mitophagy, and mitochondria–endoplasmic reticulum contact sites crosstalk under hypoxia. Frontiers in cell and developmental biology. 2022 Feb 25;10:848214.https://doi.org/10.3389/fcell.2022.848214

94. Westermann B. Mitochondrial fusion and fission in cell life and death. Nature reviews Molecular cell biology. 2010 Dec;11(12):872-84.https://doi.org/10.1038/nrm3013

95. Ganguly G, Chakrabarti S, Chatterjee U, Saso L. Proteinopathy, oxidative stress and mitochondrial dysfunction: cross talk in Alzheimer's disease and Parkinson's disease. Drug design, development and therapy. 2017 Mar 16:797-810.https://doi.org/10.2147/DDDT.S130514

96. Chu CT. A pivotal role for PINK1 and autophagy in mitochondrial quality control: implications for Parkinson disease. Human molecular genetics. 2010 Apr 15;19(R1):R28-37.https://doi.org/10.1093/hmg/ddq143

97. Tanaka K. The PINK1–Parkin axis: an overview. Neuroscience research. 2020 Oct 1;159:9-15.https://doi.org/10.1016/j.neures.2020.01.006

98. Kowalczyk P, Sulejczak D, Kleczkowska P, Bukowska-Ośko I, Kucia M, Popiel M, Wietrak E, Kramkowski K, Wrzosek K, Kaczyńska K. Mitochondrial oxidative stress—a causative factor and therapeutic target in many diseases. International journal of molecular sciences. 2021 Dec 13;22(24):13384. https://doi.org/10.3390/ijms222413384

99. Picca A, Guerra F, Calvani R, Romano R, Coelho-Júnior HJ, Bucci C, Marzetti E. Mitochondrial dysfunction, protein misfolding and neuroinflammation in Parkinson's disease: roads to biomarker discovery. Biomolecules. 2021 Oct 13;11(10):1508.https://doi.org/10.3390/biom11101508

100. Haque ME, Akther M, Azam S, Kim IS, Lin Y, Lee YH, Choi DK. Targeting α-synuclein aggregation and its role in mitochondrial dysfunction in Parkinson's disease. British Journal of Pharmacology. 2022 Jan;179(1):23-45. https://doi.org/10.1111/bph.15684

101. Vasquez V, Kodavati M, Mitra J, Vedula I, Hamilton DJ, Garruto RM, Rao KS, Hegde ML. Mitochondria-targeted oligomeric α-synuclein induces TOM40 degradation and mitochondrial dysfunction in Parkinson's disease and parkinsonism-dementia of

Guam. Cell Death & Disease. 2024 Dec 18;15(12):914.https://doi.org/10.1038/s41419-024-07258-5

102. Napolitano G, Fasciolo G, Venditti P. Mitochondrial management of reactive oxygen species. Antioxidants. 2021 Nov 17;10(11):1824. https://doi.org/10.3390/antiox10111824

103. Stowe DF, Camara AK. Mitochondrial reactive oxygen species production in excitable cells: modulators of mitochondrial and cell function. Antioxidants & redox signaling. 2009 Jun 1;11(6):1373-414.https://doi.org/10.1089/ars.2008.2331

104. Martinez TN, Greenamyre JT. Toxin models of mitochondrial dysfunction in Parkinson's disease. Antioxidants & redox signaling. 2012 May 1;16(9):920-34.https://doi.org/10.1089/ars.2011.403

105. Kim-Han JS, Antenor-Dorsey JA, O'Malley KL. The parkinsonian mimetic, MPP+, specifically impairs mitochondrial transport in dopamine axons. Journal of Neuroscience. 2011 May 11;31(19):7212-21.https://doi.org/10.1523/JNEUROSCI.0711-11.2011

106. Fonck C, Baudry M. Rapid reduction of ATP synthesis and lack of free radical formation by MPP+ in rat brain synaptosomes and mitochondria. Brain research. 2003 Jun 13;975(1-2):214-21.https://doi.org/10.1016/S0006-8993(03)02675-1

107. Agnihotri A, Aruoma OI. Alzheimer's disease and Parkinson's disease: a nutritional toxicology perspective of the impact of oxidative stress, mitochondrial dysfunction, nutrigenomics and environmental chemicals. Journal of the American College of Nutrition. 2020 Jan 2;39(1):16-27.https://doi.org/10.1080/07315724.2019.1683379

108. Carmo C, Naia L, Lopes C, Rego AC. Mitochondrial dysfunction in Huntington's disease. Polyglutamine disorders. 2018 Feb 10:59-83.https://doi.org/10.1007/978-3-319-71779-1_3

109. Satapathy T, Sahu D, Sahu H, Pandey RK, Shukla SS, Gidwani B. Trends on Nanomedicines as Novel therapeutics Approach in Targeting Nociceptors for Relieving Pain. Current Drug Targets. 2024 Sep; 25(12):796-818. https://doi.org/10.2174/0113894501315521240725065617

110. Gualtieri R, Kalthur G, Barbato V, Di Nardo M, Adiga SK, Talevi R. Mitochondrial dysfunction and oxidative stress caused by cryopreservation in reproductive cells. Antioxidants. 2021 Feb 24;10(3):337.https://doi.org/10.3390/antiox10030337

111. Oliveira JM. Nature and cause of mitochondrial dysfunction in Huntington's disease: focusing on huntingtin and the striatum. Journal of neurochemistry. 2010 Jul;114(1):1-2. https://doi.org/10.1111/j.1471-4159.2010.06741.x

112. Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1α is a master regulator of mitochondrial lifecycle and ROS stress response. Antioxidants. 2023 May 10;12(5):1075.https://doi.org/10.3390/antiox12051075

113. Scarpulla RC. Nucleus-encoded regulators of mitochondrial function: integration of respiratory chain expression, nutrient sensing and metabolic stress. Biochimica et Biophysica Acta (BBA)-Gene Regulatory Mechanisms. 2012 Sep 1;1819(9-10):1088-97.https://doi.org/10.1016/j.bbagrm.2011.10.011

114. Intihar TA, Martinez EA, Gomez-Pastor R. Mitochondrial dysfunction in Huntington's disease; interplay between HSF1, p53 and PGC-1α transcription factors. Frontiers in cellular neuroscience. 2019 Mar 19;13:103.https://doi.org/10.3389/fncel.2019.00103

115. Jurcau A, Jurcau CM. Mitochondria in Huntington's disease: implications in pathogenesis and mitochondrial-targeted therapeutic strategies. Neural Regeneration Research. 2023 Jul 1;18(7):1472-7.https://doi.org/10.4103/1673-5374.360289

116. Abu Shelbayeh O, Arroum T, Morris S, Busch KB. PGC-1α is a master regulator of mitochondrial lifecycle and ROS stress response. Antioxidants. 2023 May 10;12(5):1075. https://doi.org/10.1155/2020/1452696

117. Palabiyik AA, Palabiyik E. Pharmacological approaches to enhance mitochondrial biogenesis: focus on PGC-1A, AMPK, and SIRT1 in cellular health. Molecular Biology Reports. 2025 Dec;52(1):270.https://doi.org/10.1139/apnm-2020-0005

118. Vercruysse P, Vieau D, Blum D, Petersén Å, Dupuis L. Hypothalamic alterations in neurodegenerative diseases and their relation to abnormal energy metabolism. Frontiers in molecular neuroscience. 2018 Jan 19;11:2.https://doi.org/10.3389/fnmol.2018.00002

119. Satapathy T, Kumar D. A comprehensive review and recent advancement in the application of tannins for treating Parkinson disease. Pharmacological Research-Modern Chinese Medicine. 2024 Sep 1; 12:100499. https://doi.org/10.1016/j.prmcm.2024.100499

120. BYGRAVE FL. Mitochondria and the control of intracellular calcium. Biological Reviews. 1978 Feb;53(1):43-79.https://doi.org/10.1111/j.1469-185X.1978.tb00992.x

121. Endlicher R, Drahota Z, Štefková K, Červinková Z, Kučera O. The mitochondrial permeability transition pore—current knowledge of its structure, function, and regulation, and optimized methods for evaluating its functional state. Cells. 2023 Apr 27;12(9):1273.https://doi.org/10.3390/cells12091273

122. Bonora M, Patergnani S, Ramaccini D, Morciano G, Pedriali G, Kahsay AE, Bouhamida E, Giorgi C, Wieckowski MR, Pinton P. Physiopathology of the permeability transition pore: molecular mechanisms in human pathology. Biomolecules. 2020 Jul 4;10(7):998. https://doi.org/10.3390/biom10070998

123. Cai J, Yang J, Jones D. Mitochondrial control of apoptosis: the role of cytochrome c. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 1998 Aug 10;1366(1-2):139-49.https://doi.org/10.1016/S0005-2728(98)00109-1

124. Dolgacheva LP, Zinchenko VP, Goncharov NV. Molecular and cellular interactions in pathogenesis of sporadic Parkinson disease. International journal of molecular sciences. 2022 Oct 27;23(21):13043.https://doi.org/10.3390/ijms232113043

125. Tafuri F, Ronchi D, Magri F, Comi GP, Corti S. SOD1 misplacing and mitochondrial dysfunction in amyotrophic lateral sclerosis pathogenesis. Frontiers in cellular neuroscience. 2015 Aug 25;9:336.https://doi.org/10.3389/fncel.2015.00336

126. Bauer TM, Murphy E. Role of mitochondrial calcium and the permeability transition pore in regulating cell death. Circulation research. 2020 Jan 17;126(2):280-93.https://doi.org/10.1161/CIRCRESAHA.119.316306

127. Buratti E. Trends in understanding the pathological roles of TDP-43 and FUS proteins. InFrontotemporal Dementias: Emerging Milestones of the 21st Century 2021 Jan 13 (pp. 243-267). Cham: Springer International Publishing.https://doi.org/10.1007/978-3-030-51140-1_15

128. Zayani Z, Matinahmadi A, Tavakolpournegari A, Bidooki SH. Exploring Stressors: Impact on Cellular Organelles and Implications for Cellular Functions. Stresses. 2025 Apr 4;5(2):26.https://doi.org/10.3390/stresses5020026

129. Zhao WB, Sheng R. The correlation between mitochondria-associated endoplasmic reticulum membranes (MAMs) and Ca2+ transport in the pathogenesis of diseases. Acta Pharmacologica Sinica. 2025 Feb;46(2):271-91.https://doi.org/10.1038/s41401-024-01359-9

130. Jagaran K, Singh M. Nanomedicine for neurodegenerative disorders: Focus on Alzheimer's and Parkinson's diseases. International journal of molecular sciences. 2021 Aug 23;22(16):9082.https://doi.org/10.3390/ijms22169082

131. Gao XY, Yang T, Gu Y, Sun XH. Mitochondrial dysfunction in Parkinson's disease: from mechanistic insights to therapy. Frontiers in aging neuroscience. 2022 Jun 20;14:885500.https://doi.org/10.3389/fnagi.2022.885500

132. Martí iLíndez AA, Reith W. Arginine-dependent immune responses. Cellular and Molecular Life Sciences. 2021 Jul;78(13):5303-24.https://doi.org/10.1007/s00018-021-03828-4

133. Su Y. Three-Dimensional Network of Creatine Metabolism: from Intracellular Energy Shuttle to Systemic Metabolic

Regulatory Switch. Molecular Metabolism. 2025 Aug 6:102228.https://doi.org/10.1016/j.molmet.2025.102228

134. Muddapu VR, Dharshini SA, Chakravarthy VS, Gromiha MM. Neurodegenerative diseases–is metabolic deficiency the root cause? Frontiers in neuroscience. 2020 Mar 31;14:213.https://doi.org/10.3389/fnins.2020.00213

135. Correia JP, Gromicho M, Pronto-Laborinho AC, Oliveira Santos M, de Carvalho M. Creatine kinase and respiratory decline in amyotrophic lateral sclerosis. Brain Sciences. 2024 Jun 28;14(7):661.https://doi.org/10.3390/brainsci14070661

136. Cunha-Oliveira T, Montezinho L, Simões RF, Carvalho M, Ferreiro E, Silva FS. Mitochondria: a promising convergent target for the treatment of amyotrophic lateral sclerosis. Cells. 2024 Jan 29;13(3):248.https://doi.org/10.3390/cells13030248

137. Schoenmann N, Tannenbaum N, Hodgeman RM, Raju RP. Regulating mitochondrial metabolism by targeting pyruvate dehydrogenase with dichloroacetate, a metabolic messenger. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2023 Oct 1;1869(7):166769.https://doi.org/10.1016/j.bbadis.2023.166769

138. Kumar Jha M, Jeon S, Suk K. Pyruvate dehydrogenase kinases in the nervous system: their principal functions in neuronal-glial metabolic interaction and neuro-metabolic disorders. Current neuropharmacology. 2012 Dec 1;10(4):393-403.https://doi.org/10.2174/157015912804499528

139. ŠkorjaMilić N, Dolinar K, Miš K, Matkovič U, Bizjak M, Pavlin M, Podbregar M, Pirkmajer S. Suppression of pyruvate dehydrogenase kinase by dichloroacetate in cancer and skeletal muscle cells is isoform specific and partially independent of HIF-1α. International journal of molecular sciences. 2021 Aug 10;22(16):8610. https://doi.org/10.3390/ijms22168610

140. Liang R, Hou X, Zhou D, Zhu L, Teng L, Song W, Tang Q. Exercise preconditioning mitigates Ischemia-Reperfusion injury in rats by enhancing mitochondrial respiration. Neuroscience. 2024 Dec 6;562:64-74.https://doi.org/10.1016/j.neuroscience.2024.10.045

141. Zhang Y, Sun M, Zhao H, Wang Z, Shi Y, Dong J, Wang K, Wang X, Li X, Qi H, Zhao X. Neuroprotective effects and therapeutic potential of dichloroacetate: targeting metabolic disorders in nervous system diseases. International Journal of Nanomedicine. 2023 Dec 31:7559-81.https://doi.org/10.2147/IJN.S439728

142. Amorim R, Benfeito S, Teixeira J, Cagide F, Oliveira PJ, Borges F. Targeting mitochondria: the road to mitochondriotropic antioxidants and beyond. InMitochondrial biology and experimental therapeutics 2018 Mar 22 (pp. 333-358). Cham: Springer International Publishing.https://doi.org/10.1007/978-3-319-73344-9_16

143. Kaushik S, Jain P, Satapathy T, Purabiya P, Roy A. Evaluation of anti-arthritic and anti-inflammatory activities of Martynia annua L. Ethanolic extract. Clinical Phytoscience. 2021 Jan 16 ; 7(1):7. https://doi.org/10.1186/s40816-021-00250-y

144. Mishima E, Conrad M. Nutritional and metabolic control of ferroptosis. Annual Review of Nutrition. 2022 Aug 22;42:275-309.https://doi.org/10.1146/annurev-nutr-062320-114541

145. Enns GM, Kinsman SL, Perlman SL, Spicer KM, Abdenur JE, Cohen BH, Amagata A, Barnes A, Kheifets V, Shrader WD, Thoolen M. Initial experience in the treatment of inherited mitochondrial disease with EPI-743. Molecular genetics and metabolism. 2012 Jan 1;105(1):91-102.https://doi.org/10.1016/j.ymgme.2011.10.009

146. Kowaltowski AJ, Vercesi AE. Mitochondrial damage induced by conditions of oxidative stress. Free Radical Biology and Medicine. 1999 Feb 1;26(3-4):463-71.https://doi.org/10.1016/S0891-5849(98)00216-0

147. Satapathy T, Sahu D, Sahu H, Pandey RK, Shukla SS, Gidwani B. Trends on Nanomedicines as Novel therapeutics Approach in Targeting Nociceptors for Relieving Pain. Current Drug Targets. 2024 Sep; 25(12):796-818. https://doi.org/10.2174/0113894501315521240725065617

148. Cheng X, Feng D, Lv J, Cui X, Wang Y, Wang Q, Zhang L. Application prospects of triphenylphosphine-based mitochondria-targeted cancer therapy. Cancers. 2023 Jan 21;15(3):666.https://doi.org/10.3390/cancers15030666

149. Arenas-Jal M, Suñé-Negre JM, García-Montoya E. Coenzyme Q10 supplementation: Efficacy, safety, and formulation challenges. Comprehensive reviews in food science and food safety. 2020 Mar;19(2):574-94.https://doi.org/10.1111/1541-4337.12539

150. Jayatunga DP, Hone E, Khaira H, Lunelli T, Singh H, Guillemin GJ, Fernando B, Garg ML, Verdile G, Martins RN. Therapeutic potential of mitophagy-inducing microflora metabolite, urolithin A for Alzheimer's disease. Nutrients. 2021 Oct 23;13(11):3744.https://doi.org/10.3390/nu13113744

151. Iorio R, Celenza G, Petricca S. Mitophagy: molecular mechanisms, new concepts on parkin activation and the emerging role of AMPK/ULK1 axis. Cells. 2021 Dec 23;11(1):30.https://doi.org/10.3390/cells11010030

152. He L, He T, Farrar S, Ji L, Liu T, Ma X. Antioxidants maintain cellular redox homeostasis by elimination of reactive oxygen species. Cellular Physiology and Biochemistry. 2017 Nov 17;44(2):532-53.https://doi.org/10.1159/000485089

153. Zhang Q, Zhang W, Yuan X, Peng X, Hu G. Urolithin A in Central Nervous System Disorders: Therapeutic Applications and Challenges. Biomedicines. 2025 Jun 25;13(7):1553.https://doi.org/10.3390/biomedicines13071553

154. Ghosh D, Kumar A. Harnessing mitophagy for therapeutic advances in aging and chronic neurodegenerative diseases. Neuroglia. 2024 Oct 15;5(4):391-409.https://doi.org/10.3390/neuroglia5040026

155. Alegre GF, Pastore GM. NAD+ precursors nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR): potential dietary contribution to health. Current nutrition reports. 2023 Sep;12(3):445-64. https://doi.org/10.1007/s13668-023-00475-y

156. Lei P, Li W, Luo J, Xu N, Wang Y, Xie D, Guan H, Huang B, Huang X, Zhou P. PARP (Poly ADP-ribose Polymerase) Family in Health and Disease. MedComm. 2025 Sep;6(9):e70314.https://doi.org/10.1002/mco2.70314

157. Abeti R, Duchen MR. Activation of PARP by oxidative stress induced by β-amyloid: implications for Alzheimer's disease. Neurochemical research. 2012 Nov;37(11):2589-96.https://doi.org/10.1007/s11064-012-0895-x

158. Huang P, Chen G, Jin W, Mao K, Wan H, He Y. Molecular mechanisms of parthanatos and its role in diverse diseases. International journal of molecular sciences. 2022 Jun 30;23(13):7292.https://doi.org/10.3390/ijms23137292

159. Santos L, Benitez-Rosendo A, Bresque M, Camacho-Pereira J, Calliari A, Escande C. Sirtuins: the NAD+-dependent multifaceted modulators of inflammation. Antioxidants & Redox Signaling. 2023 Dec 1;39(16):1185-208.https://doi.org/10.1089/ars.2023.0295

160. Lloret A, Beal MF. PGC-1α, sirtuins and PARPs in Huntington's disease and other neurodegenerative conditions: NAD+ to rule them all. Neurochemical research. 2019 Oct;44(10):2423-34.https://doi.org/10.1007/s11064-019-02809-1

161. Di Lisa F, Carpi A, Giorgio V, Bernardi P. The mitochondrial permeability transition pore and cyclophilin D in cardioprotection. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2011 Jul 1;1813(7):1316-22.https://doi.org/10.1016/j.bbamcr.2011.01.031

162. Elrod JW, Molkentin JD. Physiologic functions of cyclophilin D and the mitochondrial permeability transition pore. Circulation Journal. 2013;77(5):1111-22.https://doi.org/10.1253/circj.CJ-13-0321

163. Stockburger C, Eckert S, Eckert GP, Friedland K, Müller WE. Mitochondrial function, dynamics, and permeability transition: a complex love triangle as a possible target for the treatment of brain aging and Alzheimer's disease. Journal of Alzheimer's

Disease. 2018 Jun 12;64(s1):S455-67.https://doi.org/10.3233/JAD-179915

164. Liao Y, Dong Y, Cheng J. The function of the mitochondrial calcium uniporter in neurodegenerative disorders. International journal of molecular sciences. 2017 Feb 10;18(2):248.https://doi.org/10.3390/ijms18020248

165. Sun L, Wei H. Ryanodine receptors: a potential treatment target in various neurodegenerative disease. Cellular and molecular neurobiology. 2021 Nov;41(8):1613-24.https://doi.org/10.1007/s10571-020-00936-w

166. Grattagliano I, Di Ciaula A, Baj J, Molina-Molina E, Shanmugam H, Garruti G, Wang DQ, Portincasa P. Protocols for mitochondria as the target of pharmacological therapy in the context of nonalcoholic fatty liver disease (NAFLD). Mitochondrial Regulation: Methods and Protocols. 2021 Jun 7:201-46.https://doi.org/10.1007/978-1-0716-1433-4_12

167. Sen K, Satapathy T. Efficient and Safe Induction of Diabetes in Experimental Animals: A Review on Alternative Models and Techniques. Journal of Lab Animal Research. 2024 Oct 31; 3(5):27-39. https://doi.org/10.58803/jlar.v3i5.47

168. Vaughan RA, Mermier CM, Bisoffi M, Trujillo KA, Conn CA. Dietary stimulators of the PGC-1 superfamily and mitochondrial biosynthesis in skeletal muscle. A mini-review. Journal of physiology and biochemistry. 2014 Mar;70(1):271-84.https://doi.org/10.1007/s13105-013-0301-4

169. Dasgupta A, Chen KH, Wu D, Hoskin V, Mewburn J, Lima PD, Parlow LR, Hindmarch CC, Martin A, Sykes EA, Tayade C. An epigenetic increase in mitochondrial fission by MiD49 and MiD51 regulates the cell cycle in cancer: Diagnostic and therapeutic implications. The FASEB Journal. 2020 Apr;34(4):5106-27.https://doi.org/10.1096/fj.201903117R

170. Ruiz A, Alberdi E, Matute C. Mitochondrial division inhibitor 1 (mdivi-1) protects neurons against excitotoxicity through the modulation of mitochondrial function and intracellular Ca2+ signaling. Frontiers in Molecular Neuroscience. 2018 Jan 17;11:3.https://doi.org/10.3389/fnmol.2018.00003

171. Li M, Li CM, Ye ZC, Huang J, Li Y, Lai W, Peng H, Lou TQ. Sirt3 modulates fatty acid oxidation and attenuates cisplatin-induced AKI in mice. Journal of Cellular and Molecular Medicine. 2020 May;24(9):5109-21.https://doi.org/10.1111/jcmm.15148

172. Cacabelos R, Carril JC, Cacabelos N, Kazantsev AG, Vostrov AV, Corzo L, Cacabelos P, Goldgaber D. Sirtuins in Alzheimer's disease: SIRT2-related genophenotypes and implications for pharmacoepigenetics. International journal of molecular sciences. 2019 Mar 12;20(5):1249.https://doi.org/10.3390/ijms20051249

173. Chen L, Qin Y, Liu B, Gao M, Li A, Li X, Gong G. PGC-1 α-mediated mitochondrial quality control: molecular mechanisms and implications for heart failure. Frontiers in cell and developmental biology. 2022 May 27;10:871357.https://doi.org/10.3389/fcell.2022.871357

174. Wang Y, Liu N, Lu B. Mechanisms and roles of mitophagy in neurodegenerative diseases. CNS neuroscience & therapeutics. 2019 Jul;25(7):859-75.https://doi.org/10.1111/cns.13140.

175. Chen LB. Mitochondrial membrane potential in living cells. Annual review of cell biology. 1988 Nov;4(1):155-81.https://doi.org/10.1146/annurev.cb.04.110188.001103

176. Yang J, Griffin A, Qiang Z, Ren J. Organelle-targeted therapies: a comprehensive review on system design for enabling precision oncology. Signal transduction and targeted therapy. 2022 Nov 19;7(1):379.https://doi.org/10.1038/s41392-022-01243-0

177. Satapathy T, Sahu D, Sahu H, Pandey RK, Shukla SS, Gidwani B. Trends on Nanomedicines as Novel therapeutics Approach in Targeting Nociceptors for Relieving Pain. Current Drug Targets. 2024 Sep; 25(12):796-818. https://doi.org/10.2174/0113894501315521240725065617

178. Zahariev N, Boyuklieva R, Penkov D, Lukova P, Katsarov P. Functionalized Magnetic Nanoparticles: Can They Revolutionize the Treatment of Neurodegenerative Disorders? Materials. 2025 Sep 14;18(18):4302.https://doi.org/10.3389/fimmu.2024.1451989

179. Murphy MP, Smith RA. Targeting antioxidants to mitochondria by conjugation to lipophilic cations. Annu. Rev. Pharmacol. Toxicol.. 2007 Feb 10;47(1):629-56.https://doi.org/10.1146/annurev.pharmtox.47.120505.105110

180. Matés JM, Sánchez-Jiménez FM. Role of reactive oxygen species in apoptosis: implications for cancer therapy. The international journal of biochemistry & cell biology. 2000 Feb 1;32(2):157-70.https://doi.org/10.1016/S1357-2725(99)00088-6

181. Satapathy T, Panda PK, Mishra G. Comparative Evaluation of in Vitro Antioxidant, Amylase Inhibition and Cytotoxic Activity of Cur-Pip Dual Drug Loaded Nanoparticles. InAdvances in Biomedical Engineering and Technology: Select Proceedings of ICBEST 2018 2020 Sep 29 (pp. 129-139). Singapore: Springer Singapore. https://doi.org/10.1007/978-981-15-6329-4_12

182. Singh D. A sojourn on mitochondria targeted drug delivery systems for cancer: Strategies, clinical and future prospects. Mitochondrion. 2024 Jan 1;74:101826.https://doi.org/10.1016/j.mito.2023.101826

183. Song M, Ye L, Yan Y, Li X, Han X, Hu S, Yu M. Mitochondrial diseases and mtDNA editing. Genes & Diseases. 2024 May 1;11(3):101057.https://doi.org/10.1016/j.gendis.2023.06.026

184. Yang Y, Wu H, Kang X, Liang Y, Lan T, Li T, Tan T, Peng J, Zhang Q, An G, Liu Y. Targeted elimination of mutant mitochondrial DNA in MELAS-iPSCs by mitoTALENs. Protein & cell. 2018 Mar;9(3):283-97.https://doi.org/10.1007/s13238-017-0499-y

185. Torres AK, Jara C, Llanquinao J, Lira M, Cortés-Díaz D, Tapia-Rojas C. Mitochondrial bioenergetics, redox balance, and calcium homeostasis dysfunction with defective ultrastructure and quality control in the Hippocampus of aged female C57BL/6J mice. International Journal of Molecular Sciences. 2023 Mar 13;24(6):5476. https://doi.org/10.3390/ijms24065476

186. Li CL, Liu JF, Liu SF. Mitochondrial dysfunction in chronic obstructive pulmonary disease: unraveling the molecular nexus. Biomedicines. 2024 Apr 7;12(4):814.https://doi.org/10.3390/biomedicines12040814

187. Liang X, Kristiansen CK, Vatne GH, Hong Y, Bindoff LA. Patient-specific neural progenitor cells derived from induced pluripotent stem cells offer a promise of good models for mitochondrial disease. Cell and tissue research. 2020 Apr;380(1):15-30.https://doi.org/10.1007/s00441-019-03164-x

188. Liu S, Liang Q. Sepsis toxicity network reconstruction—Dynamic signaling and multi-organ injury: A review. Biomolecules and Biomedicine. 2025 Sep 2.https://doi.org/10.17305/bb.2025.12931

189. Hu SY, Zhuang QQ, Qiu Y, Zhu XF, Yan QF. Cell models and drug discovery for mitochondrial diseases. Journal of Zhejiang University-SCIENCE B. 2019 May;20(5):449-56.https://doi.org/10.1631/jzus.B1900196

190. Milani L, Ghiselli F. Faraway, so close. The comparative method and the potential of non-model animals in mitochondrial research. Philosophical Transactions of the Royal Society B. 2020 Jan 20;375(1790):20190186.https://doi.org/10.1098/rstb.2019.0186

191. Hong L, Sklar LA. Targeting GTPases in Parkinson's disease: comparison to the historic path of kinase drug discovery and perspectives. Frontiers in molecular neuroscience. 2014 Jun 5;7:52.https://doi.org/10.3389/fnmol.2014.00052