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The Role of Oxidative Stress in Causing Mitochondrial Dysfunction Article Review

R.A.Hussein [1] , Sabreen Yahya Ghaeeb *[1]Awsaf Ibrahim mustafa[2]

[1*] Department of Biology, College of Sciences, University of Kirkuk

[2] Collage of pharmacy, Kirkuk university, Kirkuk, Iraq

rand_abdulraheem@uokirkuk.edu.iq

Sabren-yahya@uokirkuk.edu.iq

awsafibrahim@uokirkuk.edu.iq

I. Abstract

Background: Mitochondria are vital organelles involved in ATP synthesis via oxidative phosphorylation (OXPHOS). The term oxidative stress refers to the condition of imbalance between ROS production and the antioxidative capacity of an organism. This review aims to outline recent findings regarding the mechanisms underlying oxidative stress-caused mitochondrial dysfunction. Specifically, the following topics will be discussed: damage to ETC, mtDNA mutations, depolarization of mitochondrial membranes, and mitochondrial apoptosis. ***Methods***: A systematic review of scientific articles was performed using Pubmed, Scopus, Web of Science, and Google Scholar databases for papers published between 2010 and 2024. In accordance with the PRISMA guidelines (2020), a total of 58 peer-reviewed articles were used after their screening and analysis. These were clinical randomized controlled trials, in vivo animal studies, and in vitro experiments. ***Results & Conclusions***: There is sufficient evidence that mitochondria-mediated OXPHOS leads to the formation of ROS, resulting in a feedback cycle in which ROS damage to ETC causes further ROS production. The key targets include Complex I (NADH dehydrogenase), mtDNA (D-loop region), cardiolipin, and mPTP. ROS damage to mitochondria can underlie various pathologies, including neurodegenerative, metabolic, cardiovascular diseases, and aging. Thus, targeting mitochondria via MitoQ, SS-31, SkQ1 may represent an effective approach.

Keywords: Reactive Oxygen Species (ROS); Mitochondrial Dysfunction; Oxidative Phosphorylation (OXPHOS); Electron Transport Chain (ETC); Mitochondrial DNA (mtDNA); Antioxidant Therapies; MitoQ; Apoptosis; Neurodegeneration; Metabolic Syndrome

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https://iasj.rdd.edu.iq/journals/journal/issue/20226 https://doi.org/10.54174/utjagr.v13ii 232.

II. Introduction

The mitochondrion is a double-membraned organelle that exists in almost all eukaryotic cells to provide energy by producing around 90% of the total cellular ATP using oxidative phosphorylation (OXPHOS), apart from ATP production, mitochondria are also involved in regulating calcium balance, apoptosis, thermogenesis, and redox balance. Hence, maintenance of mitochondrial integrity is essential for cellular function and survival (1).

Oxidative stress is defined as an imbalance between reactive oxygen species (ROS) generation and cell's antioxidant capabilities, at physiological levels, the mitochondrial electron transport chain (ETC) generates a certain amount of ROS including superoxide ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2), the latter serves important signaling functions such as activating genes and inducing inflammation. In case of excessive generation of ROS caused by different factors, there would be oxidative stress, leading to numerous adverse effects (2).

Since mitochondria produce ROS and at the same time are damaged by them, it creates a vicious cycle where ROS affect OXPHOS activity, increasing further ROS production. The following article will analyze the knowledge about the initiation and development of oxidative stress-induced mitochondrial dysfunction, its causes and consequences, as well as potential therapies (3).

Major Objectives of This Review
▸ To highlight the key mechanisms that lead to mitochondrial dysfunction through oxidative stress.
▸ To elucidate the cascade of pathology from ETC damage to mitochondria dysfunction.
▸ To discuss the role of mitochondrial oxidative dysfunction in human diseases.
▸ To provide a review on mitochondrial oxidative therapy.
▸ To pinpoint the research gap in current studies.

2.2 Inclusion & Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
✓ Peer-reviewed articles (2010–2024)	✗ Review articles, editorials, and letters
✓ Studies in English language	✗ Studies published before 2010
✓ Mechanistic, in vitro, in vivo, or clinical studies	✗ Non-English language publications
✓ Direct investigation of ROS-mitochondria interactions	✗ Studies without measurable ROS or mitochondrial endpoints
✓ Studies with quantitative or semi-quantitative	✗ Low-quality studies (Newcastle-Ottawa score < 4)

University of Thi-Qar Journal of agricultural research

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outcomes ✓ Human, animal, or cell-line models	✗ Conference abstracts without full-text

2. Methodology – PRISMA Approach

2.1 Literature Search

A literature search was performed in January 2024 in four leading databases for scientific studies: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The use of the following search algorithm is highlighted below: ("oxidative stress" OR "reactive oxygen species" OR "ROS") AND ("mitochondrial dysfunction" OR "mitochondria" OR "electron transport chain" OR "OXPHOS") AND ("mechanism" OR "pathway" OR "signaling") (4).

2.3 PRISMA Flow Diagram

PRISMA STAGE	Details & Numbers
Identification	Database search: PubMed (n = 890), Scopus (n = 612), Web of Science (n = 448), Google Scholar (n = 350). Total number: n = 2,300.
Screening	Duplicates removed: n = 580. Screening based on title/abstract: n = 1,720. Exclusion based on irrelevant topic: n = 1,420. Total remaining: n = 300.
Eligibility	Full-text assessed: n=300. Excluded after full-text review: n=242 (reviews n=98, non-English n=44, poor quality n=100). Eligible: n=58
Included	Final articles included in synthesis: n=58. Study types: RCT (n=12), in vitro (n=21), in vivo (n=14), clinical cohort (n=11)

Figure 1. PRISMA 2020 Flow Diagram — Article selection process for this systematic review

3. Mitochondria and ROS Production

3.1 Mitochondrial Structure and OXPHOS

The IMM houses the ETC, which consists of five protein complexes (I-V). These complexes sequentially reduce NADH/FADH2 and transfer electrons to molecular oxygen, resulting in proton (H+) transportation across IMM, forming electrochemical gradient of protons ($\Delta\Psi m$, ≈−180 mV). Complex V (ATP synthase) harnesses this potential difference and converts ADP into ATP, generating roughly 30-32 ATPs per glucose molecule (5).

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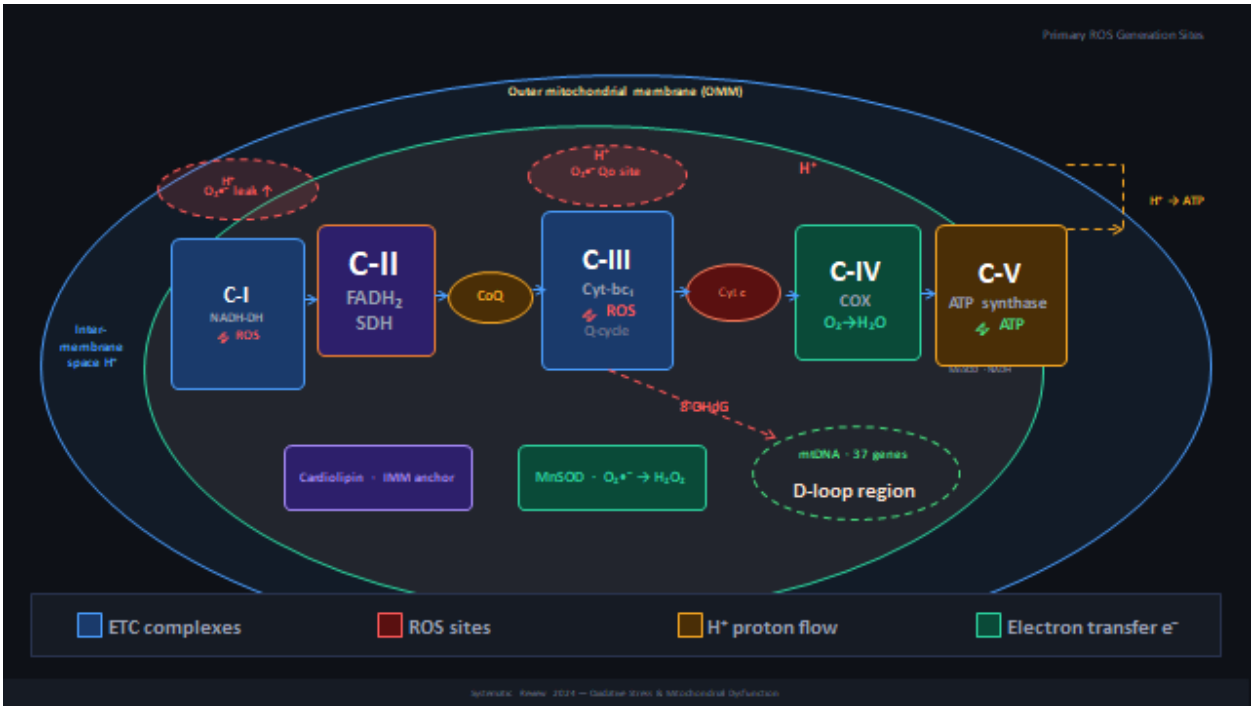

Fig. 1 — Mitochondrial Structure & ETC Complexes

3.2 Sources of ROS from Mitochondria

Under normal physiological conditions, about 1-2% of electrons escape along the respiratory chain and are converted into ROS, specifically superoxide radical (O2•−), the main sites for electron leakage are Complex I (via flavin mononucleotide and ubiquinone sites) and Complex III (ubisemiquinone site via Q-cycle), other mitochondrial ROS sources include α-KGDH, PDH, and MAO-A/B on the outer mitochondrial membrane (6).

ROS Species	Chemical Formula	Primary Source	Reactivity Level
Superoxide	O2•−	Complex I & III electron leak	Moderate
Hydrogen Peroxide	H2O2	SOD dismutation of O2•−	Low (diffusible)
Hydroxyl Radical	OH•	Fenton / Haber-Weiss reaction	Extremely High

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Peroxynitrite	ONOO−	O2•− + NO•	Very High
Singlet Oxygen	1O2	Photosensitization	High
Hypochlorous Acid	HOCl	Neutrophil myeloperoxidase	High

Table 1. Major reactive oxygen species: chemical identity, mitochondrial source, and relative reactivity

3.3 Mitochondrial Antioxidant Defenses

The mitochondria have an elaborate antioxidant defense system to protect against ROS attacks. MnSOD/SOD2 located in the mitochondrial matrix converts superoxide radicals into hydrogen peroxide, which then undergoes detoxification via GPx or Prx-3 using GSH. Thioredoxin-2/thioredoxin reductase-2 and catalase, predominantly found in peroxisomes, but with mitochondrial isoforms in certain cell types, further strengthen antioxidant defense mechanisms. Once ROS formation exceeds the capacity of the above antioxidative systems, oxidative stress develops (7, 8).

1	**Electron Leak**	Electrons escape from Complexes I & III during ATP synthesis → O2 reduction to superoxide (O2•−)
	Superoxide Formation	Superoxide dismutase (SOD) converts O2•− → H2O2; excess leads to OH• via Fenton reaction
	Lipid Peroxidation	ROS attacks mitochondrial membrane phospholipids → MDA, 4-HNE formation → membrane integrity loss
	mtDNA Damage	OH• induces 8-OHdG lesions in mitochondrial DNA → mutations in ETC subunit genes → complex dysfunction
	ETC Impairment	Damaged ETC complexes reduce electron efficiency → increased ROS production (vicious cycle)
	ΔΨm Collapse	Loss of mitochondrial membrane potential → impaired ATP synthesis → energy crisis
	Apoptosis Signal	Cytochrome c release → caspase activation → programmed cell death or necrosis

Figure 2. Stepwise Mechanistic Pathway: From Electron Leak to Mitochondrial Failure and Cell Death

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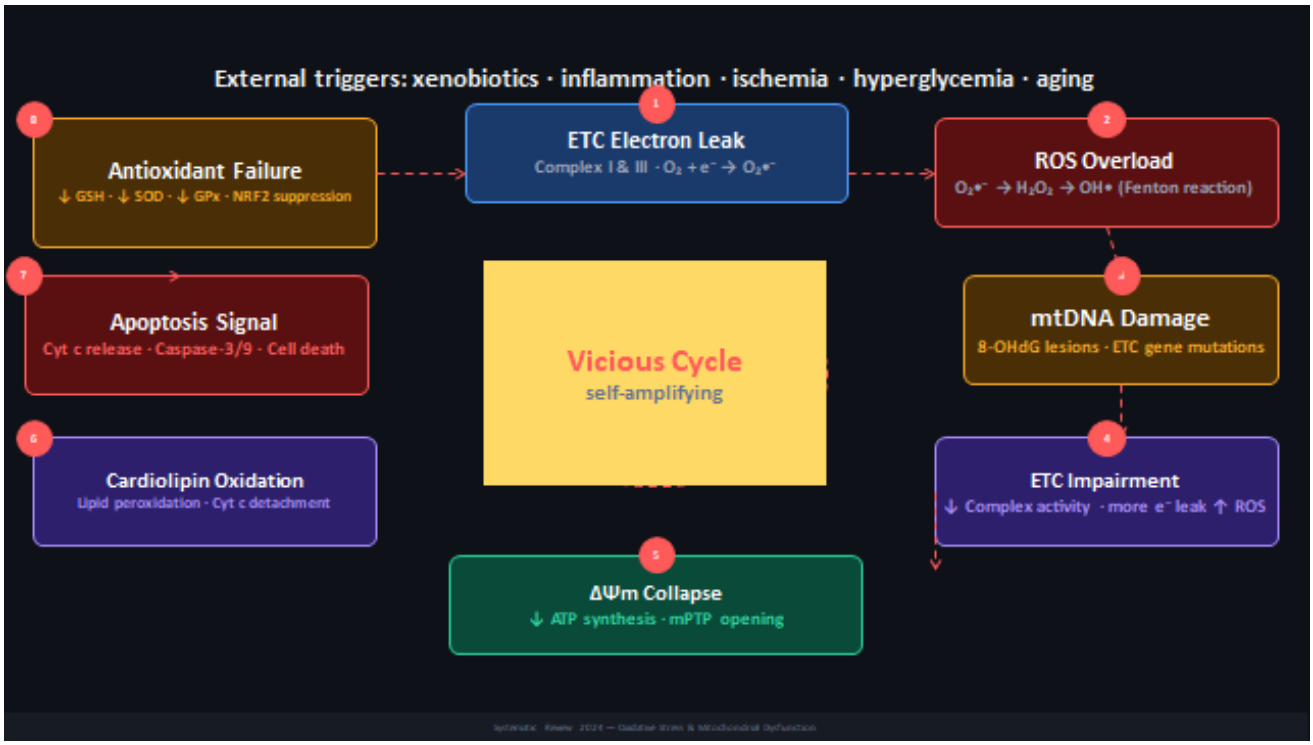
4.2 Dysfunction of ETC Complexes

Complex I (NADH:ubiquinone oxidoreductase) is the largest of all ETC complexes, with the greatest ROS generation potential. ROS-induced oxidation of Complex I iron-sulfur clusters and ND subunits of mtDNA triggers increased electron leakage. Experimental evidence shows that Complex I inhibition through 4-HNE, a product of lipid peroxidation, causes about a 40–60% reduction in NADH oxidation. Complex III malfunction, caused by superoxide generated at the Qo site, disrupts the Q-cycle, resulting in electron transport from ubiquinone towards oxygen, not cytochrome c (9).

Fig. 2 : The Self-Amplifying ROS–Mitochondrial Dysfunction Cycle



4.3 Mitochondrial DNA Damage

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In contrast to nuclear DNA, mtDNA does not have protective histones and possesses minimal repair mechanisms; hence, it is 10–20 times more prone to oxidative damage than nuclear DNA, ROS-triggered formation of 8-oxo-2'-deoxyguanosine (8-OHdG) is the most common type of oxidative damage, which causes G:C→T:A transversion mutations, the D-loop region of mtDNA, which controls mtDNA replication and transcription, is especially susceptible, increased mutations in mtDNA decrease the ratio of ETC components, gradually deteriorating the capacity of OXPHOS (**10**).

4.4 Cardiolipin Peroxidation and Membrane Disruption

Cardiolipin (CL) is a distinctive dimeric phospholipid that is only present in IMM and is crucial for maintaining the structure and function of all five ETC complexes and ANT. Its four polyunsaturated fatty acid tails are the preferred targets for ROS-induced peroxidation. As oxidized cardiolipin (oxCL) can no longer sustain the proper supercomplex assembly of ETC complex (respirasome), its ability to transfer electrons is reduced by up to 30%, and cytochrome c is readily detached, initiating intrinsic apoptosis (**11**).

4.5 Mitochondrial Permeability Transition Pore (mPTP) Opening

Mitochondrial permeability transition pore (mPTP) is a large conductance, non-selective ion channel within IMM that becomes activated when ROS levels are high, there is calcium overload, and ΔΨm is reduced, once open, mPTP allows molecules with up to 1,500 Da to permeate through IMM, dissipating the proton gradient and ΔΨm, this causes ATP synthesis inhibition and mitochondria swelling, leading to the rupture of mitochondrial OM and release of pro-apoptotic proteins (cytochrome c, AIF, Smac/DIABLO) into the cytosol, ultimately committing the cell to apoptosis (**12**).

5. Mitochondrial Oxidative Dysfunction as a Cause of Human Diseases

Mechanisms described above are the foundation of many human diseases. It should be emphasized that mitochondrial oxidative dysfunction is not just an epiphenomenon – increasing amount of data suggest its role as one of major causative agents during disease development (**13**) **.**

Disease / Condition	Primary ROS Source	Mitochondrial Target	Key Biomarkers
Alzheimer's Disease	Aβ-induced ETC dysfunction	Complex I & IV	8-OHdG, MDA, Cytochrome c

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Parkinson's Disease	Dopamine oxidation	Complex I (NADH dehydrogenase)	DJ-1, α-synuclein, H2O2
Type 2 Diabetes	Hyperglycemia, AGEs	mtDNA, Complex II	Malondialdehyde, SOD activity
Cardiovascular Disease	Xanthine oxidase, NOX	ETC Complexes, mPTP	ROS flux, ΔΨm, ATP/ADP ratio
Nonalcoholic Fatty Liver	Lipid oxidation (β-oxidation)	OXPHOS, mtDNA	4-HNE, Cytochrome c, ALT
Cancer	Oncogene-driven ROS	TCA cycle enzymes	HIF-1α, VEGF, mtROS
Aging	Accumulative ETC leak	mtDNA mutations	Telomere shortening, 8-OHdG
Sepsis	Inflammatory NOX activation	Complex IV	NO•, ONOO−, ATP collapse

Table 2. Diseases associated with oxidative stress-induced mitochondrial dysfunction: mechanisms and markers

5.1 Neurodegenerative Diseases

Despite the fact that the brain accounts for approximately 2% of body weight, it consumes about 20% of oxygen in our body, making neurons prone to oxidative mitochondrial damage, during the development of Alzheimer's disease (AD) amyloid-beta peptides incorporate into mitochondrial membrane, blocking activities of Complexes I, II, and IV, and stimulating the generation of hydrogen peroxide. Mitochondrial dysfunction precedes neuron loss and may be considered as one of mechanisms behind the 'mitochondrial cascade hypothesis' of AD. Complex I inhibition (found in 30–40% of Parkinson's disease (PD) patients with substantia nigra lesions) and α-synuclein-mediated mitochondria fragmentation lead to dopaminergic neuron death in PD (14).

5.2 Metabolic Syndrome/Type 2 Diabetes

Continuous exposure of mitochondria to high glucose concentrations induces generation of ROS via three mechanisms: increased NADH/FAD redox activity, AGEs action via RAGE receptor, and mitophagy impairment. All of this contributes to the occurrence of mitochondrial dysfunction in insulin-sensitive tissues (skeletal muscle,

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liver, adipose tissue). Mitochondrial dysfunction results in impairment of glucose transport and fat metabolism, which further enhances insulin resistance (**15**).

5.3 Cardiovascular Disease

Mitochondria take up 25-30% of cell volume in case of cardiomyocytes due to extremely high energy requirements of these cells, the ischemia/reperfusion injury (IRI) exemplifies oxidative mitochondrial dysfunction: restoration of oxygen supply after the period of ischemia causes oxidative burst that results in opening of mPTP channels, consequently, cardiomyocyte apoptosis significantly exceeds ischemic insult, excessive production of ROS in heart failure is caused by NADPH oxidases (NOX2, NOX4) and xanthine oxidase (**16**).

6. Therapeutic Approaches for Mitochondria Oxidative Stress

6.1 Justification of Targeting Mitochondria

Traditional systemic antioxidants (vitamins C and E) have been ineffective in clinical trials of various diseases associated with oxidative stress, since their therapeutic levels cannot accumulate in mitochondria, therefore, the justification for MTAs seems reasonable, as the local effect of a drug directly aimed at mitochondria would be much more effective (**17**).

6.2 Existing Therapeutic Options

6.3 The Working Mechanisms of Most Promising Compounds

MitoQ (Mitoquinone Mesylate)

The main component of MitoQ is a conjugate consisting of a ubiquinone covalently attached to TPP+ (tri phenyl phosphonium). Due to the presence of an electron acceptor, the cation accumulates 500-1000 times within mitochondrial matrix due to ΔΨm potential. As a result, MitoQ works as a redox cycle: it constantly alternates between ubiquinone and ubiquinol and scavenges radicals. In clinical Phase II trials for Parkinson's and nonalcoholic fatty liver diseases, it proved to be safe and effective in reducing mtDNA damage biomarkers (**18**).

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SS-31 (Elamipretide)

The drug consists of a tetrapeptide (D-Arg-2′,6′-dimethylTyr-Lys-Phe-NH2) and binds cardiolipin molecules in the IMM. Consequently, SS-31 prevents oxidation and subsequent cytochrome c dissociation, thereby preserving proper ETC structure. In Phase II clinical trials in Barth syndrome patients (cardiolipin deficiency), it demonstrated the ability to increase exercise tolerance and improve cardiovascular functioning (**19**).

Mitochondrial Biogenesis Enhancers

In addition to antioxidants, the stimulation of mitochondrial biogenesis leads to a reduction in damaged mitochondrial elements. One such compound, PGC-1α, acts as the principal factor in mitochondrial production and biogenesis. Resveratrol, NAD+ (NMN, NR), exercise increase activity of SIRT1-PGC-1α axis (**20**).

7. Summary of Key Findings

KEY FINDINGS
1. Complex I and Complex III of the mitochondrial electron transport chain are the main locations for physiological and pathological ROS formation, with superoxide (O2•−) being the earliest radical involved in the oxidative cascade.
2. ROS damage to mtDNA targets mainly the D-loop regulatory segment and genes of respiratory subunits; the result is an autoregulatory cycle involving increased ROS generation and respiratory chain dysfunction.
3. Cardiolipin oxidation is a critical step that precedes other forms of oxidative mitochondrial dysfunction, including impaired ETC supercomplex structure, cytochrome c release from membranes, and induction of apoptosis.
4. Permeabilization of the mPTP is a decisive stage when mitochondrial failure under oxidative stress is inevitable; it causes ΔΨm collapse, depletes ATP stores, and leads to cell death.
5. Oxidative damage to mitochondria causes a variety of diseases, including AD and PD, T2D, CVD, NAFLD, and organismal aging.
6. Mitochondrial-targeted antioxidants (MTOs) like MitoQ, SS-31, and SkQ1 show higher efficiency compared to systemic agents because of their ability to accumulate 500-1000 times higher in mitochondria.
7. Defective mitophagy associated with chronic oxidative stress promotes accumulation of damaged mitochondria and further amplifies cellular ROS levels in a self-enhancing manner.
8. Induction of the SIRT1-PGC-1α-NRF2 transcription network can be another therapeutic approach to enhance

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mitochondrial biogenesis while boosting endogenous antioxidants.

8. Knowledge Gaps and Directions for Future Research

Notwithstanding considerable progress, several knowledge gaps still hinder the development of clinically effective treatments, (**21, 22, 23**).

Knowledge Gaps Identified and Future Research Needs
‣ Tissue Specificity: The vast majority of the studies described were performed using cell lines or rodents. The degree to which mitochondrial oxidative dysfunction contributes to tissue pathology in human patients requires additional study through the use of patient-specific organoids and single-cell transcriptomics.
‣ Temporal Specificity: Thresholds for ROS above which they initiate damage rather than physiological effects remain unknown; longitudinal studies employing ROS monitoring with imaging techniques are needed.
‣ Optimizing MTA Administration: Both MitoQ and SS-31 have promising preclinical data; however, optimal doses, routes of administration, and inclusion/exclusion criteria for clinical application need to be established.
‣ Mitophagy Pharmacology: The role played by selective mitophagy and its threshold in response to increased mitochondrial ROS remains largely uninvestigated. Novel classes of mitophagy activators can potentially be used as therapeutic drugs.
‣ Sex and Age Specificity: Data indicates that the way mitochondria handle ROS differs among sexes and changes throughout the course of one's life; clinical trials should factor in those differences.
‣ Multiple Omics Approach: By combining the results from transcriptomic, proteomic, metabolomic, and mtDNA sequencing, greater mechanistic resolution will be obtained compared to when a single approach is taken.
‣ Combining Therapeutics: Combination treatment with MTAs, NAD+ precursors, and mitophagy activators theoretically shows promise; however, there are no appropriate clinical trials to confirm that.

Conclusion

A systematic review conducted herein reveals that oxidative stress is not only associated with mitochondrial dysfunction, but it is a central mechanism of action, acting through several connected pathways. Oxidative stress triggers a series of downstream mechanisms involving ROS-mediated oxidative modifications of ETC complexes, mitochondrial DNA mutations, lipid oxidation of cardiolipin, and permeability transition pore

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opening leading to impaired mitochondrial energy metabolism, decreased mitochondrial membrane integrity, and cellular apoptosis.

The vicious cycle of mitochondrial ROS production and subsequent oxidative damage to ETC components is an important hurdle that complicates the treatment of oxidative stress-related disorders. The continuous worsening of neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, type 2 diabetes, and heart failure following mitochondrial damage despite the absence of initial stressors can be explained by the presence of this feedback loop.

The introduction of mitochondria-targeted antioxidants is a breakthrough in the approach towards oxidative stress and mitochondrial dysfunctions compared to conventional antioxidant drugs. Mitochondria-targeted drugs deliver the active component directly to the site of ROS formation, overcoming problems with bioavailability encountered in systemic antioxidants that failed in clinical trials. MitoQ, SS-31, and other molecules have been proven safe and effective in preliminary studies; however, randomized controlled trials of Phase III scale are required to confirm their benefits for patients with specific diseases.

Fig. 3 — Disease Spectrum & Mitochondria-Targeted Therapies

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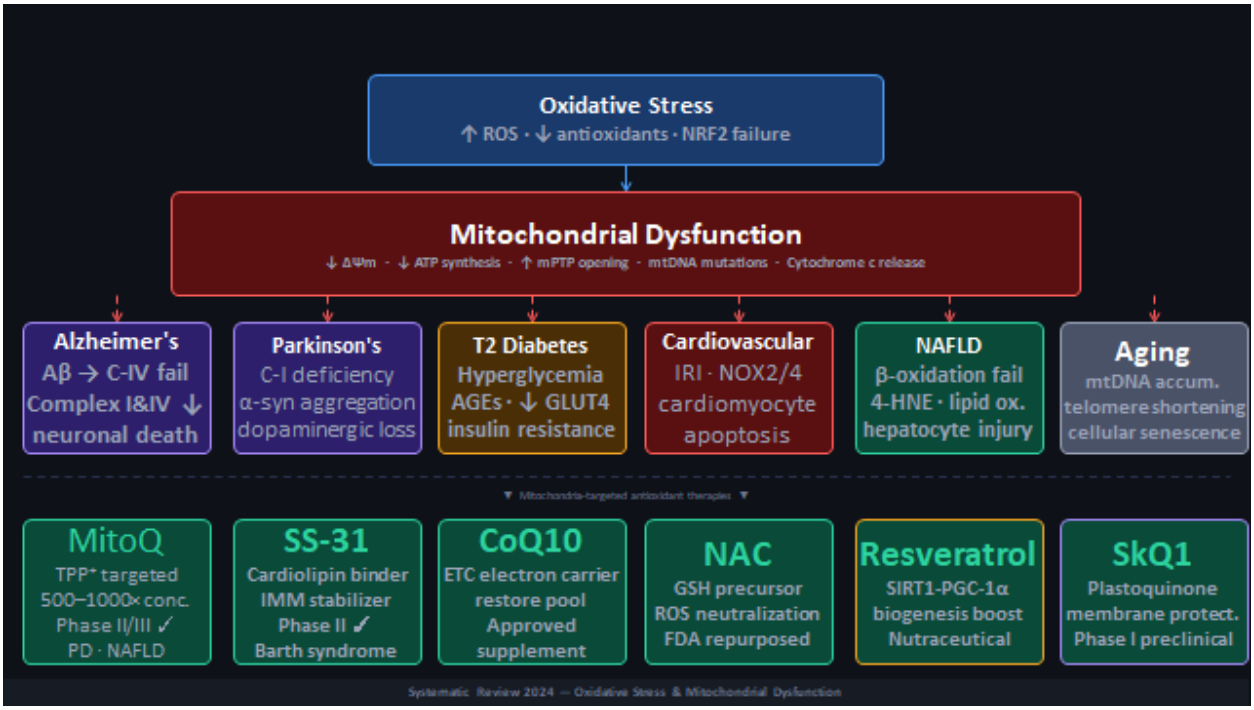

Combination therapy seems to be a promising strategy for the treatment of mitochondrial dysfunctions and associated disorders. The approach involves using MTA compounds, mitophagy inducers, PGC-1α and NRF2 activators, and precision medicine techniques for targeting specific patient populations. Elucidating the link between oxidative stress and mitochondrial dysfunction is one of the most significant achievements in the field of modern medical science.

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