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Mitochondrial Dysfunction Induced by Hyperglycemia as a Key Mechanism in Metabolic Disorders

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ABSTRACT

Background: Hyperglycemia is a major feature of metabolic disorders and is closely associated with mitochondrial dysfunction through oxidative stress, impaired bioenergetics, and altered mitochondrial regulation. Plant-derived bioactive compounds have also attracted interest for their potential to modulate these mitochondrial and redox pathways. **Objectives:** This review aimed to synthesize published evidence on hyperglycemia-induced mitochondrial dysfunction as a central mechanism in metabolic disorders and to summarize the potential role of plant-derived compounds in modulating mitochondrial pathways. **Methods:** This study was conducted as a narrative literature review. Articles were searched through PubMed, SAGE Journals, and ScienceDirect databases for publications from 2015 to 2025. The search terms included combinations of hyperglycemia, mitochondrial dysfunction, oxidative stress, PGC-1α, Nrf2, mitochondrial biogenesis, mitochondrial dynamics, metabolic disorders, and plant-derived extracts. Eligible articles included original studies and review papers discussing mitochondrial alterations under hyperglycemic conditions in in vitro, animal, or human studies. The data were synthesized qualitatively and organized into thematic categories without meta-analysis. **Discussion:** Hyperglycemia increases reactive oxygen species (ROS) production, impairs electron transport chain efficiency, and reduces adenosine triphosphate (ATP) generation. It may also disturb mitochondrial quality control by promoting excessive fission and suppressing PGC-1α-mediated mitochondrial biogenesis. Oxidative stress–responsive pathways, including Nrf2, contribute to mitochondrial redox homeostasis under metabolic stress. Polyphenols, flavonoids, and curcumin may modulate these pathways by activating Nrf2-dependent antioxidant responses and supporting mitochondrial biogenesis-related signaling. **Conclusion:** Hyperglycemia contributes to mitochondrial dysfunction through oxidative stress, impaired energy metabolism, and altered mitochondrial regulatory pathways. Plant-derived compounds may offer potential protective effects, although many studies remain limited by the lack of direct mitochondrial functional assessment.
Keyword: hyperglycemia; mitochondrial dysfunction; Nrf2; oxidative stress; PGC-1α

ABSTRAK

Latar Belakang: Hiperglikemia merupakan ciri utama gangguan metabolik dan berhubungan erat dengan disfungsi mitokondria melalui stres oksidatif, gangguan bioenergetika, dan perubahan regulasi mitokondria. Senyawa bioaktif berbasis tanaman juga mendapat perhatian karena berpotensi memodulasi jalur mitokondria dan redoks tersebut. **Tujuan:** Tinjauan ini bertujuan untuk menyintesis bukti ilmiah mengenai disfungsi mitokondria akibat hiperglikemia sebagai mekanisme penting pada gangguan metabolik, serta merangkum potensi

senyawa berbasis tanaman dalam memodulasi jalur mitokondria. **Metode:** Studi ini disusun sebagai *narrative literature review*. Penelusuran artikel dilakukan melalui basis data PubMed, SAGE Journals, dan ScienceDirect untuk publikasi tahun 2015 hingga 2025. Kata kunci yang digunakan mencakup kombinasi *hyperglycemia, mitochondrial dysfunction, oxidative stress*, PGC-1α, Nrf2, *mitochondrial biogenesis, mitochondrial dynamics, metabolic disorders, dan plant-derived extracts*. Artikel yang memenuhi kriteria meliputi penelitian asli dan artikel review yang membahas perubahan mitokondria pada kondisi hiperglikemia berdasarkan studi in vitro, hewan coba, maupun manusia. Data disintesis secara kualitatif dan disusun dalam kategori tematik tanpa meta-analisis. **Pembahasan:** Hiperglikemia meningkatkan produksi reactive oxygen species (ROS), menurunkan efisiensi rantai transpor elektron, dan mengurangi pembentukan adenosine triphosphate (ATP). Kondisi ini juga dapat mengganggu kontrol kualitas mitokondria dengan meningkatkan fisi berlebihan dan menekan biogenesis mitokondria yang dimediasi PGC-1α. Jalur respons stres oksidatif, termasuk Nrf2, berperan dalam menjaga homeostasis redoks mitokondria selama stres metabolik. Senyawa fitokimia seperti polifenol, flavonoid, dan kurkumin berpotensi memodulasi jalur tersebut melalui aktivasi respons antioksidan bergantung Nrf2 dan dukungan terhadap regulasi biogenesis mitokondria. **Kesimpulan:** Hiperglikemia berkontribusi terhadap disfungsi mitokondria melalui stres oksidatif, gangguan metabolisme energi, dan perubahan jalur regulasi mitokondria. Senyawa berbasis tanaman berpotensi memberikan efek protektif, meskipun banyak studi masih terbatas karena belum mengevaluasi fungsi mitokondria secara langsung.
Keyword: disfungsi mitokondria; hiperglikemia; Nrf2; PGC-1α; stres oksidatif

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1. Introduction

Metabolic disorders, particularly diabetes mellitus and related metabolic syndromes, remain a major global health burden and are commonly characterized by persistent hyperglycemia and systemic metabolic dysregulation.[1–3] Alongside well-known metabolic consequences, recent literature increasingly highlights that chronic hyperglycemia can trigger cellular dysfunction that contributes to disease progression and complications.[3,4] In this context, mitochondria have gained attention as a key intracellular target because they play a central role in energy production, redox balance, and stress responses in metabolically active tissues.[5,6]

Hyperglycemia is closely associated with mitochondrial dysfunction through several interconnected mechanisms. Elevated glucose levels promote oxidative stress and excessive production of reactive oxygen species (ROS), which can impair mitochondrial components and reduce electron transport chain efficiency, ultimately decreasing adenosine triphosphate (ATP) generation.[7,8] Mitochondrial oxidative damage is also strongly associated with the development of diabetic complications, particularly through pathways that amplify cellular injury and inflammatory responses.[6,9] Overall, these findings indicates that mitochondrial dysfunction is not only a consequence of metabolic imbalance but also contributes to the progression of metabolic disorders.[6,8]

In addition to bioenergetic disturbances, hyperglycemia can disrupt mitochondrial quality control mechanisms, including mitochondrial dynamics (fission and fusion) and mitochondrial turnover. Recent studies and reviews indicate that an imbalance in fission–fusion regulation contributes to mitochondrial fragmentation, reduced mitochondrial efficiency, and increased cellular susceptibility to metabolic stress.[10–12] These changes are considered relevant mechanisms in diabetes-related tissue injury and microvascular complications, making mitochondrial dynamics a potential therapeutic target. [12,13]

Hyperglycemia has also been associated with reduced mitochondrial biogenesis, which limits mitochondrial renewal and metabolic flexibility. Pathways involving peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) are frequently described as central regulators of mitochondrial biogenesis and broader mitochondrial quality control.[14–16] When these pathways are suppressed, mitochondrial content and function may decline, further worsening cellular stress responses and energy imbalance under chronic hyperglycemic conditions.[14,16]

Oxidative stress–responsive signaling pathways, particularly the Keap1/Nrf2/ARE axis, also play an

important role in maintaining mitochondrial redox homeostasis during metabolic stress. Recent evidence suggests that Nrf2 activity supports antioxidant defense and may help limit oxidative injury in diabetes-related conditions, while disruption of this signaling can contribute to persistent oxidative stress and tissue damage. This makes Nrf2-related pathways relevant not only for understanding disease mechanisms but also for identifying potential intervention targets.[17–19]

Recent studies suggest that mitochondrial dysfunction associated with hyperglycaemia may be partially modifiable. Several reviews and experimental studies describe the potential of plant-derived bioactive compounds (including polyphenols and flavonoids) to influence mitochondrial pathways by supporting antioxidant defenses and mitochondrial regulation, including Nrf2 signaling and mitochondrial biogenesis-related pathways.[20–23] However, many intervention studies still emphasize metabolic outcomes, while direct assessment of mitochondrial function (e.g., respiratory capacity, ATP production, or integrated bioenergetic endpoints) is less consistently reported, indicating an opportunity for more mechanistically integrated designs in future work.[22]

Accordingly, this narrative literature review aims to synthesize current evidence on hyperglycemia-induced mitochondrial dysfunction as a key mechanism underlying metabolic disorders. Particular emphasis is placed on mitochondrial bioenergetics, oxidative stress, mitochondrial dynamics, mitochondrial biogenesis (including PGC-1α-related regulation), and Nrf2-dependent redox signaling, while also summarizing evidence on plant-derived interventions as mechanistically relevant approaches.

2. Method

This study was conducted as a narrative literature review to synthesize published evidence on hyperglycemia-induced mitochondrial dysfunction as a central mechanism in metabolic disorders. The review also summarized literature addressing plant-derived interventions with potential modulatory effects on mitochondrial pathways under hyperglycemic conditions.

Literature searches were performed using PubMed, SAGE Journals, and ScienceDirect databases for articles published between 2015 and 2025. Search terms included combinations of hyperglycemia, mitochondrial dysfunction, metabolic disorders, oxidative stress, PGC-1α, Nrf2, mitochondrial biogenesis, mitochondrial dynamics, and plant-derived extracts. Additional relevant articles were identified through manual screening of reference lists.

Eligible publications included original research articles and review papers that discussed the mechanistic relationship between hyperglycemia, mitochondrial dysfunction, and metabolic disorders based on evidence from in vitro, animal, and human studies. Studies were selected if they provided clear explanations of mitochondrial alterations, including changes in mitochondrial function, oxidative stress, biogenesis, or dynamics under hyperglycemic conditions. Articles that did not specifically address mitochondrial mechanisms or lacked relevance to hyperglycemia-related metabolic disturbances were excluded. The collected data were synthesized qualitatively and organized into thematic categories to highlight common mechanistic pathways, without performing a quantitative meta-analysis.

3. Result and Discussion

3.1 Hyperglycemia-Induced Mitochondrial Dysfunction in Metabolic Disorders

Persistent hyperglycemia has been consistently associated with impaired mitochondrial homeostasis in several metabolically active tissues, including skeletal muscle, liver, pancreas, and kidney. Under prolonged high-glucose exposure, mitochondrial metabolism becomes overloaded, resulting in increased electron leakage from the electron transport chain and excessive formation of reactive oxygen species (ROS).[24,25] The accumulation of mitochondrial ROS can trigger oxidative injury to key cellular components, such as mitochondrial DNA, proteins, and membrane lipids, thereby compromising mitochondrial integrity and function.

These oxidative effects reduce the efficiency of oxidative phosphorylation, leading to lower adenosine triphosphate (ATP) production and disruption of cellular energy balance. Several studies have reported that hyperglycemic conditions are linked to decreased mitochondrial respiratory capacity and altered electron transport chain activity, further contributing to oxidative stress and metabolic imbalance.[24] As a result, insulin-sensitive tissues experience impaired glucose uptake, changes in lipid metabolism, and reduced

metabolic flexibility.

Mitochondrial abnormalities under hyperglycemic conditions are not limited to functional changes but also involve structural alterations. Experimental findings describe changes such as disrupted cristae structure, mitochondrial swelling, and reduced mitochondrial membrane potential in cells exposed to chronic hyperglycemia.[24] These structural changes are associated with decreased mitochondrial efficiency and a higher susceptibility to cell damage.

Overall, these mitochondrial alterations are closely linked to the development of insulin resistance and pancreatic β-cell dysfunction. Evidence also suggests that mitochondrial dysfunction may occur early in metabolic disease, indicating that mitochondrial impairment contributes to disease development rather than being only a consequence of prolonged glucotoxicity.[22,24]

No	Author & Year	Model/Study Context	Mitochondrial Pathway Investigated	Main Findings	Relevance
1	Chen et al., 2025	Experimental and clinical diabetes models	Mitochondrial quality control (PGC-1α-mediated biogenesis, fusion–fission balance, mitophagy, mtROS)	Chronic hyperglycemia disrupts mitochondrial quality control through excessive ROS production, impaired biogenesis, and altered mitochondrial dynamics	Provides a comprehensive mechanistic framework linking hyperglycemia to mitochondrial dysfunction
2	Rodríguez et al., 2023	Endothelial cells exposed to acute high glucose	Mitochondrial dynamics (DRP1, OPA1), bioenergetics	Hyperglycemia induces mitochondrial fragmentation and reduces ATP production	Supports the role of mitochondrial structural alterations in early metabolic dysfunction
3	Tang et al., 2024	Diabetic retinopathy model	DRP1-dependent mitochondrial fission and mtROS	Excessive fission and oxidative stress mediate cellular injury under hyperglycemia	Identifies mitochondrial dynamics as a therapeutic target in diabetes complications
4	Nwakiban et al., 2020	HepG2 cells treated with plant extracts	Nrf2-mediated antioxidant response	Plant extracts activate Nrf2 signaling and improve glucose uptake	Demonstrates plant-derived modulation of oxidative stress pathways
5	Clemente-Suárez et al., 2025	Metabolic disorders	PGC-1α/SIRT1/TFAM-driven mitochondrial biogenesis	Plant antioxidants enhance mitochondrial efficiency and redox balance	Supports plant-based interventions targeting mitochondrial dysfunction
6	Ebrahimi et al., 2025	Diabetes and metabolic syndrome	Polyphenol–Nrf2–mitochondrial axis	Polyphenols reduce oxidative stress and preserve mitochondrial integrity	Reinforces Nrf2 as a protective pathway in hyperglycemia
7	Rampin et al., 2022	Redox-related metabolic diseases	KEAP1–Nrf2/ARE signaling	Natural compounds activate Nrf2 antioxidant defense	Provides mechanistic basis for Nrf2-targeted therapy

Table 1. Key Literature on Hyperglycemia-Associated Mitochondrial Dysfunction and Natural Product-Based Interventions.

3.2 Alterations in Mitochondrial Dynamics and Biogenesis under Hyperglycemic Conditions

Mitochondrial dynamics, which include the processes of fission and fusion, play an important role in maintaining mitochondrial quality and supporting cellular adaptation to metabolic stress. Studies have shown that hyperglycemia disrupts this balance by increasing mitochondrial fission and reducing fusion activity. This condition is marked by increased activation of dynamin-related protein 1 (DRP1) and reduced

expression of mitofusins (MFN1 and MFN2), leading to mitochondrial fragmentation.[25,26]

Fragmented mitochondria tend to produce less ATP and generate higher levels of ROS, which further worsens oxidative stress. In hyperglycemic models, increased DRP1-mediated fission has been associated with reduced mitochondrial membrane potential, impaired respiratory function, and increased cellular sensitivity to metabolic stress.[26] These findings indicate that changes in mitochondrial dynamics significantly affect mitochondrial function during hyperglycemia.

In addition to altering mitochondrial dynamics, chronic hyperglycemia may also impair mitochondrial biogenesis. This effect is partly mediated through suppression of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a key regulator of mitochondrial formation and energy metabolism. Reduced PGC-1α expression can downregulate its downstream targets, including nuclear respiratory factors and mitochondrial transcription factor A (TFAM), leading to decreased mitochondrial content and reduced capacity for mitochondrial renewal.[24,27]

Disruption of both mitochondrial dynamics and biogenesis weakens mitochondrial quality control, limiting the ability of cells to replace damaged mitochondria and adjust to metabolic demands. This condition contributes to reduced metabolic adaptability and highlights the importance of mitochondrial regulation in maintaining metabolic stability under chronic hyperglycemic conditions.

3.3 Plant-Derived Extracts as Modulators of Mitochondrial Function

In addition to their metabolic effects, plant-derived extracts have been reported to influence mitochondrial function by modulating signaling pathways related to oxidative stress and energy metabolism. Experimental studies indicate that various phytochemical compounds, particularly polyphenols and flavonoids, can modulate nuclear factor erythroid 2–related factor 2 (Nrf2) signaling and enhance cellular antioxidant defenses under metabolic stress. Extracts of Cameroonian spices such as *Xylopia parviflora*, *Echinops giganteus*, and *Dichrostachys glomerata* have been reported to reduce intracellular reactive oxygen species (ROS) in HepG2 cells. Nrf2 involvement has also been demonstrated for selected extracts, particularly *X. parviflora*, which was associated with increased nuclear Nrf2 levels. [28,29]

Activation of the Nrf2 pathway contributes to cellular antioxidant defense and may help maintain redox and mitochondrial homeostasis under metabolic stress. At the molecular level, oxidative or electrophilic signals modify redox-sensitive residues in Keap1, thereby reducing Nrf2 ubiquitination and degradation and allowing Nrf2 to accumulate and translocate to the nucleus. Nuclear Nrf2 then heterodimerizes with small Maf proteins and binds to antioxidant response elements (AREs), promoting the transcription of cytoprotective and antioxidant genes, including HO-1, NQO1, and enzymes involved in glutathione metabolism. This response may help limit excessive ROS accumulation and maintain cellular redox balance. [22]

Several plant-derived bioactive compounds have also been reported to influence pathways involved in mitochondrial biogenesis, including PGC-1α, sirtuin 1 (SIRT1), and mitochondrial transcription factor A (TFAM). Modulation of these pathways has been associated with mitochondrial biogenesis, energy metabolism, and redox regulation in experimental models of diabetes and metabolic stress.[27]

Although interest in medicinal plants as potential modulators of mitochondrial function continues to grow, many studies still focus mainly on metabolic or antioxidant outcomes. Direct and integrated evaluation of mitochondrial biogenesis, dynamics, bioenergetics, and quality control remains relatively limited. Further mechanistic studies incorporating direct mitochondrial parameters alongside conventional metabolic measurements are therefore needed to clarify the extent to which plant-derived interventions may contribute to the maintenance or improvement of mitochondrial homeostasis.

3.4 Translational Implications and Future Research Directions.
Overall, the reviewed literature indicates that mitochondrial dysfunction is a key and potentially modifiable mechanism linking hyperglycemia to metabolic disorders.[24] Alterations in mitochondrial energy metabolism, dynamics, biogenesis, and redox regulation are consistently observed across experimental models and clinical studies.

While plant-derived interventions show promising effects on mitochondrial-related pathways, future studies would benefit from more integrated experimental designs that assess mitochondrial dynamics, biogenesis, and oxidative stress together.[22,27] Such approaches may help clarify how these interventions influence mitochondrial quality control.

Future research should therefore focus on experimental strategies that evaluate mitochondrial structure, function, and redox balance alongside conventional metabolic parameters. This approach is important to determine whether plant-derived interventions can improve mitochondrial homeostasis, rather than only reducing hyperglycemia, and to support the development of mitochondrial-based strategies for managing metabolic disorders.

4. Conclusion

This literature review indicates that mitochondrial dysfunction is closely associated with hyperglycemia and may contribute to the development and progression of metabolic disorders. Prolonged exposure to high glucose levels is associated with impaired mitochondrial energy metabolism, increased oxidative stress, altered mitochondrial dynamics, and reduced mitochondrial biogenesis, which together may compromise cellular energy balance and metabolic function.

Evidence from experimental and clinical studies suggests that mitochondrial abnormalities may occur relatively early in the course of metabolic disease, supporting the possibility that mitochondrial dysfunction is involved in disease progression rather than being solely a consequence of metabolic imbalance. Alterations in regulatory pathways, particularly PGC-1α-related mitochondrial biogenesis and Nrf2-dependent antioxidant signaling, further suggest an important role for mitochondrial regulation in cellular responses to metabolic and oxidative stress under hyperglycemic conditions.

The reviewed literature also suggests that some hyperglycemia-associated mitochondrial alterations may be modifiable, including through plant-derived compounds that influence antioxidant defense, redox regulation, and mitochondrial-related pathways. However, many studies continue to emphasize metabolic or antioxidant outcomes, while direct assessment of mitochondrial structure and function remains limited. Future studies integrating mitochondrial bioenergetics, dynamics, quality control, and oxidative stress with conventional metabolic parameters are therefore needed to clarify whether these interventions can improve mitochondrial homeostasis beyond their effects on hyperglycemia.

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