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Role of Natural Products in Targeting Mitochondrial Dysfunction and Energy Metabolism in Obesity-Associated Diabetes

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ABSTRACT

Obesity-associated diabetes, often referred to as diabesity, is a rapidly growing global health challenge characterized by impaired glucose homeostasis, insulin resistance, and progressive mitochondrial dysfunction. Mitochondria are central regulators of energy metabolism, orchestrating glucose oxidation, lipid utilization, and ATP generation. Their dysfunction exacerbates metabolic inflexibility and oxidative stress, contributing to the pathogenesis of obesity-linked diabetes. Natural products derived from plants, marine organisms, and microbial sources have gained attention as modulators of mitochondrial function due to their bioactive compounds, including polyphenols, flavonoids, alkaloids, terpenoids, and peptides. These agents restore mitochondrial integrity, enhance oxidative phosphorylation, stimulate biogenesis, and reduce excessive reactive oxygen species, thereby improving insulin sensitivity and metabolic health. This review examines the molecular mechanisms by which natural products ameliorate mitochondrial dysfunction and modulate energy metabolism in the context of obesity-associated diabetes. Particular emphasis is placed on signaling pathways such as AMPK, PGC-1α, and SIRT1, as well as the emerging therapeutic implications of these bioactives in clinical settings.

Keywords: Natural products, Mitochondrial dysfunction, Energy metabolism, Obesity-associated diabetes, Bioactive compounds

INTRODUCTION

The increasing prevalence of obesity and type 2 diabetes mellitus (T2DM) has become a global health concern, with both conditions frequently occurring together in what is commonly termed obesity-associated diabetes or diabesity[1–4]. The interplay between excessive adiposity and dysregulated glucose metabolism establishes a vicious cycle that worsens insulin resistance, lipid accumulation, and systemic inflammation. A pivotal element underpinning these pathological processes is mitochondrial dysfunction, which contributes significantly to the disruption of cellular energy homeostasis in obesity-linked diabetes[5–9]. Mitochondria serve as metabolic hubs, orchestrating oxidative phosphorylation, lipid oxidation, and ATP production, while also regulating apoptosis and redox signaling. When mitochondrial function is compromised, cells experience a decline in energy production, an increase in reactive oxygen species (ROS), and impaired metabolic flexibility, all of which accelerate diabetic complications[10–12].

Mitochondrial dysfunction in obesity-associated diabetes is multifactorial. In adipose tissue, the excessive storage of triglycerides promotes lipotoxicity, which impairs mitochondrial oxidative capacity and drives chronic inflammation. In skeletal muscle, reduced mitochondrial density and oxidative enzyme activity limit the ability of muscle cells to efficiently utilize glucose and fatty acids, thereby exacerbating insulin resistance[11, 13–15]. The liver, another crucial metabolic organ, demonstrates impaired mitochondrial β-oxidation in obesity, leading to ectopic lipid deposition and non-alcoholic fatty liver disease, which further worsens systemic insulin sensitivity. Collectively, these alterations highlight the central role of mitochondrial dysfunction in the pathophysiology of diabesity [16].

Recent advances have identified key regulatory pathways involved in mitochondrial biogenesis and function, including AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and sirtuins such as SIRT1[17–19]. These pathways integrate nutritional,

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hormonal, and environmental cues to modulate mitochondrial turnover, oxidative phosphorylation, and antioxidant defense systems. Dysregulation of these signaling cascades is a hallmark of obesity-associated diabetes, reinforcing the need for therapeutic interventions that can restore mitochondrial health. Conventional pharmacological treatments such as metformin partly target mitochondrial function, particularly through AMPK activation. However, the long-term efficacy and safety of these agents remain limited, driving the exploration of alternative approaches, including natural product-based therapies.

Natural products, derived from medicinal plants, marine organisms, and microorganisms, have long been employed in traditional medicine for managing metabolic diseases. Modern pharmacological studies increasingly support their efficacy in modulating mitochondrial bioenergetics and energy metabolism[20–22]. Compounds such as resveratrol, curcumin, berberine, quercetin, and catechins have demonstrated the ability to activate AMPK, enhance PGC-1α-mediated mitochondrial biogenesis, and attenuate oxidative stress. For instance, resveratrol, a polyphenol found in grapes and berries, enhances mitochondrial function by activating SIRT1 and AMPK, leading to improved glucose utilization and insulin sensitivity. Similarly, berberine, an isoquinoline alkaloid, stimulates mitochondrial biogenesis and modulates lipid metabolism through AMPK activation, contributing to weight reduction and glycemic control in obese and diabetic models[23, 24].

In addition to polyphenols and alkaloids, marine-derived natural products such as fucoxanthin and astaxanthin exhibit promising bioactivities against mitochondrial dysfunction[25, 26]. These compounds reduce ROS generation, preserve mitochondrial membrane potential, and improve fatty acid oxidation. The diversity of natural bioactives and their multitargeted actions provide a unique therapeutic advantage over synthetic drugs that often address only a single metabolic defect [27, 28]. Furthermore, natural products tend to exhibit lower toxicity profiles, making them attractive candidates for long-term management of chronic diseases such as diabesity[29, 30].

Despite encouraging preclinical and clinical findings, challenges remain in translating natural products into standardized therapeutic agents. Issues related to bioavailability, pharmacokinetics, and dose optimization need to be addressed through advanced delivery systems and formulation strategies[31]. Moreover, rigorous clinical trials are required to substantiate the efficacy of these bioactive compounds in human populations with obesity-associated diabetes. Nonetheless, the potential of natural products to modulate mitochondrial dysfunction and restore metabolic homeostasis offers a compelling avenue for the development of novel therapeutic interventions[32]. This review discusses the mechanisms through which natural products target mitochondrial dysfunction and energy metabolism in obesity-associated diabetes. It highlights their impact on oxidative stress, mitochondrial biogenesis, and key regulatory pathways, and explores future directions for integrating these bioactives into clinical practice.

2. Mitochondrial Dysfunction in Obesity-Associated Diabetes

Mitochondrial dysfunction is a defining feature of obesity-associated diabetes, arising from chronic nutrient excess, insulin resistance, and systemic inflammation[12, 13, 33]. In healthy metabolic states, mitochondria flexibly switch between glucose and fatty acid oxidation to meet energy demands. However, in obesity and diabetes, this metabolic flexibility is impaired, leading to incomplete substrate oxidation, accumulation of toxic lipid intermediates, and excessive ROS production[15, 34]. These events damage mitochondrial DNA, proteins, and membranes, perpetuating a cycle of dysfunction.

In adipose tissue, dysfunctional mitochondria reduce thermogenesis and exacerbate lipid storage. Brown and beige adipocytes, normally involved in energy expenditure through uncoupling protein 1 (UCP1)-mediated thermogenesis, lose their functional capacity in obesity, reducing energy dissipation[35–38]. Skeletal muscle mitochondria, crucial for glucose uptake and fatty acid oxidation, show diminished oxidative enzyme activity and density, impairing insulin signaling. Hepatic mitochondria display reduced β-oxidation and increased lipogenesis, promoting hepatic steatosis and systemic insulin resistance.

At the molecular level, mitochondrial dysfunction in diabesity is linked to alterations in signaling pathways such as AMPK, PGC-1α, and sirtuins[39–41]. Downregulation of these regulators compromises biogenesis, reduces antioxidant defenses, and impairs oxidative phosphorylation. The resulting energetic imbalance promotes hyperglycemia, dyslipidemia, and progression of diabetic complications. Importantly, restoring mitochondrial function has been shown to improve insulin sensitivity and glucose homeostasis, underscoring its therapeutic relevance.

3. Natural Products as Modulators of Mitochondrial Function

Natural products target multiple aspects of mitochondrial dysfunction and energy metabolism in diabesity. Polyphenols such as resveratrol and quercetin stimulate AMPK and SIRT1, enhancing mitochondrial biogenesis and oxidative capacity[42–44]. Curcumin attenuates oxidative stress by upregulating antioxidant enzymes and stabilizing mitochondrial membranes[45–47]. Berberine improves mitochondrial efficiency and reduces lipid accumulation, while catechins from green tea increase fatty acid oxidation and thermogenesis.[48–50]

Marine bioactives like fucoxanthin and astaxanthin further expand the therapeutic repertoire. Fucoxanthin enhances mitochondrial uncoupling and promotes energy expenditure, while astaxanthin acts as a potent

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antioxidant protecting mitochondrial DNA and proteins from ROS-induced damage. These compounds improve mitochondrial membrane potential, ATP synthesis, and insulin sensitivity in preclinical models[51].
Beyond direct mitochondrial effects, natural products modulate gut microbiota, which indirectly influences mitochondrial metabolism through short-chain fatty acids and bile acid signaling. This highlights their systemic impact on metabolic regulation[52]. Together, these findings underscore the capacity of natural products to restore mitochondrial health and improve energy homeostasis in obesity-associated diabetes[52].

4. Clinical Implications and Future Directions

The therapeutic potential of natural products in targeting mitochondrial dysfunction and modulating energy metabolism in obesity-associated diabetes is increasingly recognized, yet clinical translation remains in its early stages[53]. Several small-scale clinical studies have explored the efficacy of bioactive compounds such as resveratrol, berberine, quercetin, and curcumin in improving insulin sensitivity, reducing oxidative stress, and enhancing metabolic outcomes in patients with obesity-associated diabetes[54]. Resveratrol, for instance, has been shown to improve mitochondrial biogenesis and function through activation of SIRT1 and AMPK pathways, resulting in enhanced glucose uptake, reduced inflammatory signaling, and improved lipid profiles[55, 56]. Berberine exhibits comparable benefits by modulating AMPK-mediated pathways, improving mitochondrial energy metabolism, and reducing hepatic fat accumulation[49, 54]. Quercetin and curcumin have demonstrated antioxidant and anti-inflammatory effects, protecting mitochondria from oxidative damage while promoting β-oxidation of fatty acids, thus restoring energy balance[57–59].
Despite promising results, variability in dosing regimens, bioavailability, and population characteristics poses challenges for clinical adoption. Many compounds suffer from poor absorption, rapid metabolism, and limited systemic exposure, which can reduce therapeutic efficacy[60-64]. Innovative strategies such as nanoparticle encapsulation, liposomal delivery, and structural analog development are being investigated to overcome these pharmacokinetic limitations. These approaches enhance the solubility, stability, and tissue targeting of natural compounds, potentially enabling more consistent therapeutic outcomes[65-68].
Combination therapies also offer a promising avenue, as natural products often act synergistically with conventional antidiabetic drugs[69-73]. For example, pairing AMPK-activating natural compounds with metformin may amplify effects on mitochondrial biogenesis and insulin sensitivity while mitigating drug side effects. Additionally, the multitargeted nature of natural products allows them to simultaneously address inflammation, oxidative stress, and mitochondrial dysfunction, unlike single-target pharmacological agents that may be limited in scope.
Future research should emphasize large-scale, multicenter randomized controlled trials to establish clinical efficacy and safety across diverse populations. Personalized approaches guided by nutrigenomics and metabolomics could identify individuals who are most likely to benefit from specific bioactives, enhancing precision in therapeutic interventions. Furthermore, the integration of systems biology methods will help delineate complex interactions between natural products, mitochondria, and metabolic networks, identifying novel biomarkers of response and optimizing treatment strategies.
Emerging areas, including the role of gut microbiota-derived metabolites, present additional opportunities. Natural products can modulate the gut microbiome, producing short-chain fatty acids and bile acids that influence mitochondrial function and systemic energy metabolism[74-79]. Understanding these interactions will enable more holistic interventions that target not only mitochondrial dysfunction but also its upstream regulatory networks.
In sum, the clinical implications of natural products are substantial. With continued innovation in formulation, dosing, and patient stratification, they hold the potential to complement conventional therapies, enhance mitochondrial function, and restore energy homeostasis in obesity-associated diabetes. Bridging the gap between preclinical promise and clinical application remains the key challenge for future research.

5. Challenges and Limitations in Translating Natural Products into Therapeutics

While natural products show significant promise in ameliorating mitochondrial dysfunction and restoring energy metabolism in obesity-associated diabetes, multiple challenges impede their development as standardized therapeutic agents. One of the primary limitations is poor bioavailability. Many bioactive compounds, including curcumin, resveratrol, and certain polyphenols, are hydrophobic, prone to rapid metabolism, and rapidly excreted from the body[80-84]. This pharmacokinetic limitation reduces their effective systemic concentration and therapeutic impact. Strategies to enhance absorption, such as nanoencapsulation, cyclodextrin complexes, liposomes, and prodrug derivatives, are being actively pursued, but clinical validation of these methods remains limited[85-86].
Another critical issue is variability in natural product composition. Plant-derived compounds are influenced by environmental factors such as soil quality, climate, harvesting time, and extraction methods. Consequently, the concentration of active constituents may differ between batches, posing challenges for reproducibility, standardization, and consistent efficacy in clinical settings[87-88]. Regulatory frameworks are often underdeveloped for these products, with most classified ambiguously as dietary supplements, nutraceuticals, or

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traditional medicines, which may not require the same stringent quality control as pharmaceutical drugs. Establishing standardization protocols and ensuring batch-to-batch consistency are therefore essential steps for clinical translation.

Toxicity and safety concerns also deserve careful attention. While natural products are generally perceived as safe, high doses or prolonged use may cause hepatotoxicity, nephrotoxicity, or interactions with pharmaceuticals. For example, compounds that activate AMPK or other metabolic pathways might interfere with concurrent antidiabetic medications, increasing the risk of hypoglycemia or other adverse effects. Detailed toxicological studies and interaction profiling are crucial before these agents can be recommended for widespread clinical use[69, 70]. Clinical translation is further complicated by the heterogeneity of obesity-associated diabetes. Genetic predisposition, lifestyle factors, age, and comorbidities influence individual responses to natural product interventions. Personalized medicine approaches, leveraging nutrigenomics, metabolomics, and microbiome profiling, could help tailor interventions to maximize efficacy. However, these approaches require sophisticated analytical infrastructure and validation through large, multicenter clinical trials, which are resource-intensive[71].

Finally, the mechanistic complexity of natural products presents both an advantage and a challenge. While their multitargeted actions can address multiple aspects of diabesity simultaneously, deciphering precise molecular pathways, optimal dosing regimens, and synergistic effects with other compounds remains difficult. Advanced omics technologies and computational modeling may help overcome these challenges by predicting interactions, identifying biomarkers, and guiding rational formulation of multi-compound interventions.

While natural products are promising candidates for targeting mitochondrial dysfunction and energy metabolism in obesity-associated diabetes, addressing challenges related to bioavailability, standardization, safety, clinical validation, and regulatory guidance will be essential for their successful translation into therapeutics.

CONCLUSION

Obesity-associated diabetes, characterized by insulin resistance, chronic inflammation, and mitochondrial dysfunction, presents a major global health challenge. Mitochondria, as central regulators of energy metabolism, play a critical role in maintaining cellular homeostasis through ATP production, fatty acid oxidation, and redox balance. Dysfunctional mitochondria contribute to metabolic inflexibility, oxidative stress, and progression of diabesity, highlighting mitochondrial health as a pivotal target for therapeutic intervention. Natural products, encompassing polyphenols, flavonoids, alkaloids, and marine-derived bioactives, have emerged as promising modulators of mitochondrial function, offering multifaceted benefits that extend beyond conventional pharmacological approaches. Preclinical studies demonstrate that bioactive compounds such as resveratrol, curcumin, berberine, quercetin, catechins, fucoxanthin, and astaxanthin improve mitochondrial biogenesis, restore oxidative phosphorylation, attenuate reactive oxygen species, and enhance fatty acid and glucose metabolism. These effects are mediated through key signaling pathways, including AMPK, PGC-1α, SIRT1, and Nrf2, which collectively improve energy homeostasis, insulin sensitivity, and lipid utilization. Additionally, natural products may influence mitochondrial function indirectly via modulation of gut microbiota, highlighting their systemic and integrative effects on energy metabolism. Clinical evidence, though currently limited, supports the potential of natural products to improve glycemic control, lipid profiles, and inflammatory markers in patients with obesity-associated diabetes. Resveratrol and berberine have shown particular promise in enhancing mitochondrial activity and insulin sensitivity, while polyphenols and curcumin provide antioxidant protection that stabilizes mitochondrial membranes and prevents further oxidative damage. However, challenges including poor bioavailability, inconsistent phytochemical composition, insufficient clinical trials, and potential interactions with existing medications hinder broad clinical adoption. Advanced delivery systems, formulation optimization, and rigorous standardization protocols are necessary to overcome these limitations.

In conclusion, natural products represent a compelling strategy for restoring mitochondrial function and energy balance in obesity-associated diabetes. Their multitargeted mechanisms, relative safety, and potential to complement existing therapies make them attractive candidates for long-term metabolic management. With continued research, formulation innovations, and clinical validation, natural products have the potential to transform the therapeutic landscape of diabesity, improving metabolic health, preventing complications, and enhancing quality of life for affected populations worldwide.

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