PPAR?–PGC-1a-Mediated Mitochondrial Biogenesis in Fibromyalgia: From PQQ Evaluation to Rosiglitazone Repurposing

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Fibromyalgia is a chronic disorder characterized by widespread pain, fatigue, and cognitive impairments. Current treatments primarily target symptoms rather than underlying pathology. Growing evidence implicates mitochondrial dysfunction and impaired cellular energy production in disease progression, highlighting defective mitochondrial biogenesis as a key therapeutic target. Therefore, this study investigated activation of the PPAR?–PGC-1a pathway to enhance mitochondrial biogenesis and cellular energy metabolism. Pyrroloquinoline quinone (PQQ), a known stimulator of mitochondrial biogenesis, was evaluated in differentiated C2C12 myotubes. Mitochondrial respiration was measured using Seahorse XF stress testing, while PGC-1a protein expression was assessed via Western blot. Translational feasibility was examined through molecular docking, molecular dynamics simulations, and ADMET profiling. PQQ treatment increased basal respiration by 32% and maximal respiratory capacity by 41% ($p < 0.01$), indicating enhanced oxidative phosphorylation. Moreover, PGC-1a expression increased, confirming pathway activation. However, ADMET modeling predicted 0% human oral absorption, limiting applicability. To address this limitation, rosiglitazone was evaluated as a drug-repurposing candidate. In C2C12 cells, rosiglitazone increased mitochondrial respiration, with maximal OCR rising from ~110 to ~450 pmol O2/min and upregulation of PGC-1a, indicating strong activation of mitochondrial biogenesis. It also showed high binding affinity (-10.4 kcal/mol), stable receptor engagement, and 100% predicted oral absorption, supporting its effectiveness and translational potential. These findings support a mechanism-driven, translational strategy to restore cellular energy homeostasis in fibromyalgia.

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Third Award of $1,200