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Editorial

Urolithin A-induced mitophagy: a mitochondrial therapeutic axis for decelerating musculoskeletal aging and modulating knee osteoarthritis pain

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Knee osteoarthritis (OA) is a disease characterized by cellular energy dysregulation, in which structural joint deterioration and chronic pain are caused by mitochondrial dysfunction. OA is now recognized as a multifactorial condition caused by disturbed cellular homeostasis, metabolic imbalance, and typical biological processes of aging, notably mitochondrial dysfunction. However, it was once thought to be caused by mechanical wear and cartilage degradation.[1,2]

Apoptosis, redox signaling, and cellular metabolism all depend substantially on mitochondria. It has since been recognized that mitochondrial dysfunction is a key indicator of aging, affecting inflammation, tissue deterioration, and functional decline across all organ systems [3]. Age-related decreases in the effectiveness of mitochondrial quality control systems, especially mitophagy, result in a buildup of dysfunctional mitochondria, increased reactive oxygen species (ROS), and activation of pro-inflammatory pathways. Mechanistically, the PINK1/Parkin pathway is activated during urolithin A-induced mitophagy, which makes it easier to remove damaged mitochondria and restore the integrity of the mitochondrial matrix.

Urolithin A has emerged as a biologically enticing intervention targeting mitochondrial integrity in this context. Through the metabolism of the gut microbiota, it is derived from dietary ellagitannins, stimulates mitophagy, improves mitochondrial biogenesis, and restores cellular bioenergetics. Preclinical research shows decreased oxidative stress, enhanced mitochondrial function, and decreased inflammatory signaling.[4] Because quadriceps weakness and decreased neuromuscular control enhance joint stress in knee OA, these consequences are especially pertinent.

Significantly, mitochondrial-targeted therapies have been shown to improve muscular function and metabolic resilience, supporting their clinical applicability in musculoskeletal conditions.[5]

Its integrative viability is further supported by clinical trials demonstrating increases in older adults' muscle strength, endurance, and mitochondrial biomarkers.[6] These results suggest that by strengthening the biological substrate underlying adaptability, urolithin A may improve rehabilitation outcomes. Beyond skeletal muscle, mitochondrial failure also influences extracellular matrix deterioration, synovial inflammation, and chondrocyte senescence. Urolithin A may decrease the course of OA and restore joint tissue homeostasis by encouraging mitophagy.

By reducing oxidative stress-induced nociceptive sensitization, a significant but under-studied factor in OA symptomatology, such mitochondrial restoration may also affect pain modulation. The gut microbiota converts dietary ellagitannins into urolithin A, which promotes mitochondrial biogenesis and triggers mitophagy. This lessens joint inflammation, cartilage deterioration, and chondrocyte senescence by lowering oxidative stress and inflammatory signaling (NF-κB). Improvements in skeletal muscle mitochondrial activity simultaneously

increase strength and reduce joint loading, thereby slowing the progression of OA.[7]

Additionally, urolithin A signifies a shift toward mitochondrial therapies, which focus on the biology of aging rather than just its symptoms. Combining molecular and biomechanical techniques is consistent with the precision rehabilitation paradigm. Translational issues persist, including inconsistent gut microbiota-dependent metabolism, inconsistent dosing, and a dearth of OA-specific clinical trials. In conclusion, urolithin A-induced mitophagy is a clinically promising and mechanistically sound treatment for OA. It has the potential to reduce musculoskeletal aging and enhance rehabilitation results by addressing mitochondrial dysfunction.

Urolithin A should be studied in future clinical trials as a supplement to rehabilitation, especially in early-stage OA, where cellular reversibility is most likely. Current OA therapeutic approaches risk treating symptoms rather than addressing the underlying biology of the disease if mitochondrial dysfunction is not addressed. This mitochondrial axis might define the next frontier in musculoskeletal medicine.

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